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PRINCIPAL INVESTIGATOR: Sherwood M. Reichard, Ph.D.
Robert F. Bond, Ph.D.

CONTRACTING ORGANIZATION: Medical College of Georgia
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TENTH ANNUAL CONFERENCE ON SHOCK AND FIRST INTERNATIONAL SHOCK CONGRESS

Montreal, Canada
Sunday, June 7–Thursday, June 11, 1987

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Program

Sunday, June 7

1:00 to 6:00 p.m.	Registration	Grand Salon Foyer
1:00 to 5:30 p.m.	Council Meeting	Anjou
4:00 to 6:00 p.m.	Hospitality Welcome	Grand Salon Foyer
7:00 to 8:00 p.m.	Keynote Address: **Gerald S. Moss, MD** President-Elect Michael Reese Hospital and Medical Center and University of Chicago	Grand Salons A&B
8:00 to 9:00 p.m.	Reception	Grand Salon Foyer

Monday, June 8

8:00 a.m. to 6:00 p.m.	Registration	Grand Salon Foyer
8:30 to 10:45 a.m.	Symposium I: "Cellular Aspects in Shock" Presiding: **Leena Mela-Riker, MD** Oregon Health Sciences University 1) "Mechanisms of Cell Injury in Low Flow States" **Manfred Kessler, MD** University of Erlangen, West Germany 2) "Organ Specific Metabolic Changes in Shock" **Hengo Haljamäe, MD, PhD** University of Göteborg, Sweden 3) "Metabolic Regulation in Hyperdynamic Sepsis" **Frank Cerra, MD** University of Minnesota 4) "Experimental Basis of the Management of Burns and Sepsis" **Cleon Goodwin, MD** Cornell University 5) Panel Discussion	Grand Salons A&B
10:45 to 11:45 a.m.	Poster Session I, Papers 1-51	Picardie A&B Grand Salon C Alfred Rouleau A&B
11:45 a.m. to 1:00 p.m.	Lunch Buffet	
11:45 a.m. to 1:30 p.m.	Poster Discussions 1) "Endocrinology," Papers 1-17 Chairs: **Bart Chernow, MD** Harvard Medical School and **John T. Flynn, PhD** Jefferson Medical College	Argenteuil
	2) "Endotoxin I," Papers 18-34 Chairs: **Alain Carli, MD** University Cochin Port Royal, Paris and	Grand Salon C

	John Raymond Fletcher, MD, PhD Vanderbilt University	
	3) "Circulation," Papers 35–51 Chairs: **Michael F. Wilson, MD** University of Oklahoma and **Jureta Horton, PhD** University of Texas Health Science Center, Dallas	Alfred Rouleau A&B
1:45 to 3:15 p.m.	Young Investigator Awards Session, Papers 52–55 Presiding: **Bart Chernow, MD** Harvard Medical School 1) "Prostaglandin Inhibition Impairs Renal Microvascular Blood Flow Responses During Hyperdynamic Bacteremia" **Henry M. Cryer, MD** University of Louisville (2) "Effect of Endoxtoxin (LPS) Tolerance (TOL) on Arachidonic Acid (AA) Turnover in Macrøphage (MO) Phospholipid Pools" **Tina S. Rogers, PhD** Medical University of South Carolina 3) "Prolonged Impairment of Natural Killer (NK) Cell Activity Following Simple Hemorrhage" **Rabie N. Stephan, MD** Michigan State University 4) "Hypoperfusion of the Intestinal Microcirculation During High Cardiac Output Live *E. Coli* Sepsis in Rats" **Pat W. Whitworth, MD** University of Louisville	Grand Salons A&B
3:30 to 5:30 p.m.	Paper Session I, Papers 56–63 Presiding: **Kazuo Okada, MD, PhD** Teikyo University, and **James P. Filkins, PhD** Loyola University of Chicago	Grand Salons A&B
5:30 to 6:30 p.m.	Shock Society Business Meeting Free Evening	Argenteuil

Tuesday, June 9

7:00 to 9:00 a.m.	Editorial Board *Circulatory Shock* Breakfast Meeting	Auteuil A&B
8:00 a.m. to 6:00 p.m.	Registration	Grand Salon Foyer
8:30 to 10:45 a.m.	Symposium II: "Design and Conduct of Clinical Trials" Presiding: **Lerner B. Hinshaw, PhD** University of Oklahoma, and **Peter N. Peduzzi, PhD**	Grand Salons A&B

	VA Medical Center, West Haven 1) "Statistical Design" **Peter N. Peduzzi, PhD** 2) "Design and Conduct" **Lerner B. Hinshaw, PhD** 3) "Design and Clinical Evaluation" **Charles L. Sprung, MD** University of Miami 4) Panel Discussion	
10:45 to 11:45 a.m.	Poster Session II, Papers 64–113	Picardie A&B, Grand Salon C, Alfred Rouleau A&B
11:45 a.m. to 1:00 p.m.	Buffet Lunch	
11:45 a.m. to 1:30 p.m.	Poster Discussions	
	1) "Hemorrhage I," Papers 64–79 Chairs: **Glen A. Taylor, MD** University of Toronto and **Gerald Johnson, *III*, PhD** Oral Roberts University	Argenteuil
	2) "Clinical/Burn," Papers 80–96 Chairs: **Gunther Schlag, MD** Ludwig Institute for Trauma and ***Phillip D. Toth*, MD** Methodist Hospital of Indiana	Grand Salon C
	3) "Endotoxin II," Papers 97–113 Chairs: **Maw-Shung Liu, DDS, PhD** St. Louis University and ***H. Richard Adams*, DVM, PhD** University of Missouri	Alfred Rouleau A&B
1:45 to 3:45 p.m.	Workshop I: "Septic Shock in the Young and Elderly" Presiding: **Linda Witek-Janusek, PhD** Loyola University of Chicago, and **William Schumer, MD** University of Health Sciences/ The Chicago Medical School 1) "Neonatal Sepsis: Metabolic and Hormonal Considerations" **Linda Witek-Janusek, PhD** 2) "Role of Infection in the Premature Baboon with Lung Injury" **Jacqueline J. Coalson, PhD** University of Texas, San Antonio 3) "Metabolic and Immunologic Alterations of Sepsis in the Elderly" **William Schumer, MD** 4) "Therapeutic Principles of Sepsis in the Elderly" **Daniel Rudman, MD** University of Health Sciences/ The Chicago Medical School	Grand Salons A&B

	5) "Cardiopulmonary Response of the Elderly to Trauma" **Gunther Schläg, MD** Ludwig Boltzman Institute for Trauma *Vienna, Austria* 6) Panel Discussion	
4:00 to 6:00 p.m.	Paper Session II, Papers 114–121 Presiding: **Mauricio Rocha-e-Silva, MD, PhD** University of Sao Paulo, Brazil, and **Ray Chu-Jeng Chiu, MD** McGill University	
7:00 to 8:00 p.m.	Reception	Grand Salon Foyer
8:00 to 10:00 p.m.	Dinner Speaker: **William J. Sibbald, MD** University of Western Ontario "Society and Critical Care: Interactive Responsibility Into the 1990's"	Grand Salons A&B

Wednesday, June 10

8:30 a.m. to 12:00 noon	Registration	Grand Salon Foyer
8:30 to 10:45 a.m.	Symposium III: "Humoral Mediators in Shock" Presiding: **Ulf Haglund, MD, PhD** University of Lund, Sweden 1) "Vasoactive Mediators" **Gregory B. Bulkley, MD** Johns Hopkins University 2) "Eicosanoids as Mediators" **Allan M. Lefer, PhD** Thomas Jefferson University 3) "Immunological Mediators" **Nicolas V. Christou, MD** McGill University 4) "Endotoxins as Mediators" **Iain McA. Ledingham, MD** Western Infirmary, Glasgow 5) "Other Toxic Mediators — Sources and Actions" **Ulf Haglund, MD, PhD**	Grand Salons A&B
10:45 to 11:45 a.m.	Poster Session III, papers 122–172	Picardie A&B Grand Salon C Alfred Rouleau A&B
11:45 a.m. to 1:00 p.m.	Buffet Lunch	
11:45 a.m. to 1:30 p.m.	Poster Discussions 1) "Hemorrhage II," Papers 122–138 Chairs: **Gian Paolo Novelli, MD** University of Florence and **Janet L. Parker, PhD** University of Missouri	Argenteuil

	2) "Pulmonary," Papers 139–155 Chairs: **Daniel L. Traber, PhD** University of Texas, Galveston and **Thomas Vargish, MD** West Virginia University	Grand Salon C
	3) "Endotoxin III," Papers 156–172 Chairs: **Judy A. Spitzer, PhD** Louisiana State University and **John C. Passmore, PhD** University of Louisville	Alfred Rouleau A&B
	Free Afternoon	

Thursday, June 11

8:30 a.m. to 12:00 noon	Registration	Grand Salon Foyer
8:30 to 10:45 a.m.	Symposium IV: "Central Nervous System in Shock" Presiding: **Roderick A. Little, PhD** University of Manchester, England, and **Shozo Koyama, MD, PhD** Shinshu University, Japan 1) "The Cerebral Circulation in Hypoxia and Ischemia" **Arisztid G.B. Kovach, MD** Semmelweis Medical University, Hungary 2) "Mechanisms of Direct Open (Non-Penetrating) Head Injury" **David Graham, MD** University of Glasgow, Scotland 3) "Pharmacological Protection of Brain From Hypoxia and Ischemia" **A. Wauquier, MD** Janssen Pharmaceuticals, Belgium 4) "Central Impairment of Sympathetic Outflow in Circulatory Shock" **Shozo Koyama, MD, PhD** 5) "Homostatic Reflex Function After Injury" **Roderick A. Little, PhD**	Grand Salons A&B
10:45 to 11:45 a.m.	Poster Session IV, Papers 173–218, 227	Picardie A&B Grand Salon C Alfred Rouleau A&B
11:45 a.m. to 1:00 p.m.	Buffet Lunch	
11:45 a.m. to 1:30 p.m.	Poster Discussion Sessions	
	1) "Metabolism," Papers 173–188 Chairs: **John J. Spitzer, MD** Louisiana State University and **Irshad H. Chaudry, PhD** Michigan State University	Argenteuil
	2) "Endotoxin IV," Papers 189–205 Chairs: **Mohammed M. Sayeed, PhD** Loyola University of Chicago and **W. Curtis Wise, PhD** Medical University of South Carolina	Grand Salon C

	3) "Shock/General," Papers 206–218, 227 Chairs: **David G. Reynolds, PhD** University of Iowa and **Linda T. Archer, PhD** University of Oklahoma	Alfred Rouleau A&B
1:45 to 3:45 p.m.	Workshop II: "Neuropharmacological Mechanisms and Approaches to Shock Therapy" Presiding: **John W. Holaday, PhD** Walter Reed Army Medical Center, and **Nelson J. Gurll, MD** University of Iowa 1) "Opioid-Catecholamine Interactions in Circulatory Shock" **Nelson J. Gurll, MD** 2) "Anaphylactic Shock: Catecholamine Actions in the Responses to Opioid Antagonists" **Shimon Amir, PhD** The Weizmann Institute of Science, Israel 3) "Aspects of Central and Peripheral Adrenergic Mechanisms in Experimental Shock" **Dag Lundberg, MD** University Lund, Sweden 4) "Glucagon and Calcium Involvement in Circulatory Shock and Critical Care Medicine" **Bart Chernow, MD** Harvard University 5) "Causality in Circulatory Shock: Strategies for Integrating Mediators, Mechanisms and Therapies" **Ed Neugebauer, PhD** Philipps University, Germany, and **W. Lorenz, MD** University of Marburg, West Germany	Grand Salons A&B
4:00 to 6:00 p.m.	Paper Session III, Papers 219–226 Presiding: **Hiromaru Ogata, MD** Dokhyo University, Japan, and **Francis L. Abel, MD, PhD** University of South Carolina	Grand Salons A&B
7:00 to 8:00 p.m.	Reception	Grand Salon Foyer
8:00 to 10:00 p.m.	Dinner Speaker: **Robert W. Phillips, DVM, PhD** Colorado State University and National Aeronautics and Space Administration "Biomedical Research in Space"	Grand Salons A&B

Abstracts

1 WHY DOES A HIGH CORTISOL CONCENTRATION PERSIST AFTER FRACTURE OF THE FEMORAL NECK IN THE ELDERLY? R.N. Barton* and H.B. Stoner* (Spon: R.A. Little). MRC Trauma Unit, University of Manchester, Manchester M13 9PT, U.K.

Fracture of the femoral neck is common in the elderly and recovery is often slow. The plasma cortisol concentration remains elevated for longer than in younger patients even with more severe injuries and may contribute to morbidity, for example by causing insulin resistance in muscle. In 10 patients aged 60-94 (median 74) the plasma concentration of ACTH, the expected stimulus, was at the lower end of the normal range 1 and 2 weeks after the fracture and was inappropriately low for the plasma cortisol concentration. Equilibrium dialysis showed that increased binding of cortisol to plasma proteins was not responsible for this disparity. We also examined the possibility of an impairment of cortisol clearance. The metabolic clearance rate of cortisol is known to decline with age, so that normally the same plasma cortisol concentration is maintained at a lower secretion rate. In a further 7 patients, aged 77-88, we administered [^{3}H]cortisol orally two weeks after hip fracture and measured the specific radioactivity of the major urinary cortisol metabolites. The cortisol secretion rate calculated from these data was similar to that in much younger control subjects; it was therefore higher than normal for this age group and probably appropriate to the raised plasma cortisol concentration. These results suggest that factors other than ACTH, for example other pituitary peptides or neural input, contributed to the stimulation of cortisol secretion. Similar data were obtained in a few elderly patients in a geriatric ward, suggesting that these changes were not specific to trauma.

2 ELEVATED ESTROGEN AND REDUCED TESTOSTERONE LEVELS AS INDICES OF HUMAN SEPTIC SHOCK SEVERITY. N. Christeff*, C. Benassayag*, A. Carli§, E.A. Nunez*. U. 224, INSERM - Faculté Xavier Bichat, 75018 Paris - § Service de Réanimation Polyvalente, CHU Cochin-Port-Royal, 75674 Paris, France.

The steroid and lipid concentrations in the sera of two groups of septic shock patients were studied. Group I (n=24) was in lethal shock. Group II (n=22) recovered. Both groups were compared to a control group (n=44) of healthy men. Serum estrone (E1) levels were 12 fold higher in group I than in controls (3900 $\pm$ 900 pmol/L $p < 0.001$) ; serum estradiol (E2) levels were 6 fold above control 880 $\pm$ 170 pmol/L $p < 0.001$) while serum testosterone (T) levels were much lower 11 fold (1.7 $\pm$ 0.3 nmol/L $p < 0.001$). In group II serum estrogen levels (E1 + E2) were moderately elevated, i.e. 2 fold above control (814 $\pm$ 350 pmol/L $p < 0.01$) and serum T level were lower 2 to 3 fold below control group (5.5 $\pm$ 2 nmol/L $p < 0.01$). The serum cortisol, progesterone and Δ 4 androstenedione levels were not different from control values in either group ($p < 0.05$ or NS). Groups I and II steroid levels were compared. In group I E1 ($p < 0.01$) and E2 ($p < 0.05$) were higher and T lower ($p < 0.05$) than in group II. This dramatic increase in E1 levels associated with the decrease in T suggests that the testicular and adrenal androgen aromatase activity is potentiated by glucocorticoids under these pathophysiological conditions. In contrast, triglycerides, phospholipids, cholesterol and fatty acids were significantly and equally decreased in both shock groups (I and II). The determination of E1 and T during septic shock could form the basis for pronostic estimation of shock severity.

3 CENTRAL ADMINISTRATION OF INTERLEUKIN-1 ELICITS HYPERINSULINEMIA IN RATS. Robert P. Cornell. Northeast Missouri State University, Kirksville, MO 63501.

This laboratory previously reported (Circ. Shock 18:349, 1986) that intravenous (iv) administration of human interleukin-1 (IL-1)(Collaborative Research; Lexington, MA) at a dose of 50 U produced a maximal hyperinsulinemic response at 30 min post-injection in conscious fasted rats. At that time the site of action of IL-1, either peripheral on the pancreatic beta cells or central on the fever-controlling hypothalamus, was unknown. To help resolve this uncertainty IL-1 was injected intracerebroventricularly (icv) or into the preoptic area (poa) of the anterior hypothalamus of pentobarbital-anesthetized rats. Interestingly, pentobarbital anesthesia actually enhanced the hyperinsulinemic response to 50 U of iv IL-1 (197 ± 33.5 and 41 ± 11.0 μU/ml for portal and systemic plasma, respectively, n=10) compared to the response in conscious animals (80 ± 8.0 and 25 ± 2.8 μU/ml, respectively, n=10) at 30 min postinjection probably by reducing the alpha-adrenergic suppression of insulin secretion. Plasma insulin concentrations at 20 min after 10 U IL-1 icv were 88 ± 7.6 and 26 ± 2.2 μU/ml, respectively, (n=10) and at 10 min after 5 U IL-1 poa were 125 ± 13.6 and 27 ± 4.6 μU/ml, respectively, (n=10) in pentobarbital-anesthetized fasted rats. All plasma insulin values after IL-1 icv or poa were significantly higher than following iv injection of comparable IL-1 doses or saline controls. Only the 5 U dose of IL-1 poa elicited a hyperinsulinemic response at 5 min with a concomitant hypoglycemia and hyperglucagonemia. These results suggest that a significant portion of IL-1-induced insulin secretion is mediated by unknown central mechanisms. Supported by NSF DCB-8417355.

4 SHOCK INDUCED THYROID HORMONES CHANGES.

S. Halevy, K.J. Freese,*M. Liu-Barnett,*and B.M. Altura.
SUNY - Nassau County Medical Center, E. Meadow, New York 11554 and Health Science Center at Brooklyn, New York 11203.

There is growing interest in the role of thyroid hormones in circulatory shock. This study was designed to measure 3,5,3'-triiodothyronine(T3), thyroxine(T4), free T4, and 3,3',5'-triiodothyronine (rT3) during superior mesenteric artery occlusion (SMAO) shock in the rat, a form of shock that can be quantitated. Adult male Wistar rats lightly anesthetized with pentobarbital were subjected to either 30 or 60 minute occlusions. Mean arterial blood pressure and hematocrit were measured. Blood samples were taken for thyroid hormones measurements by radioimmunoassay at 20 & 120 minutes after release of SMAO. The hematocrit was significantly elevated in all shock groups. T4 and T3 significantly decreased in the 60 minutes SMAO group and free T4 was practically unchanged. There was a four-fold increase in rT3 in the 60 minute SMAO group. These data are consistent with the progression of the shock state. The decrease in T4 and T3 and increase in rT3 was significant in the group where shock is irreversible and mortality almost 100 per cent. This is an animal model of graded shock that reflects thyroid hormone changes in a nonthyroidal stress state similar to those nonthyroidal illnesses observed in clinical conditions.

Supported by the Meadowbrook Medical Education and Research Foundation, Inc., E. Meadow, N.Y.

5 RELEASE OF GLUCAGON IN SEPTIC PATIENTS. Kimiko Ishida, Hiroshi Hayasaka, Lerner B. Hinshaw, G. Rainey Williams*. Dept. of Surgery, Univ. of Oklahoma Health Sciences Center, Oklahoma City, OK 73190 and Sapporo Medical College, Sapporo 060 Japan.

Plasma concentrations of glucagon were markedly elevated in dogs administered lethal doses of E. coli. The increase in gastrointestinal-derived glucagon was a greater magnitude than that from the pancreas (Current Surg. 42:307, 1985). We have tested the hypothesis that gastrointestinal-derived glucagon and pancreatic-derived glucagon may be released into the circulation of septic patients and may influence the pathogenesis and outcome of this disorder. The increase may be useful in determing the severity of septic patients. Plasma glucagon levels were measured in 10 patients with 4 of 7 signs of sepsis (crite-

ria designed by VA Cooperative Study No. 209 Evaluations of Corticosteroid Therapy in Gram-Negative Sepsis) and 10 healthy volunteers (control). Results are as follows (mean ± SEM, *$p < 0.05$, **$p < 0.001$ VS. control):

	CONTROL	SEPTIC PATIENTS
PANCRATIC-DERIVED GLUCAGON (pg/ml)	77±29	275±30*
GASTROINTESTINAL-DERIVED GLUCAGON (pg/ml)	85±26	3522±344**

We conclude that circulating glucagon levels increase and that the glucagon release may play a mediator / modulator role in the altered physiology of septic patients.

6 **MYOCARDIAL CONTRACTILITY AND ITS RESPONSE TO β-ADRENERGIC STIMULATION IN LACTIC ACIDOSIS.** H.Kawabata*, S.Tezuka*, M.Yahagi*, K.Mizumachi*, S.Morita* and K.Okada. Department of Anesthesiology, Teikyo University School of Medicine, 2-11-1 Kaga Itabashi-ku, Tokyo 173, Japan

Isometric contractile force of papillary muscle taken from 40 male Wistar rats (8-9 weeks old) were measured in vitro. Ten of them were used for control (Gr-c), and the other 30 were divided into 3 acidotic groups (Gr-1,Gr-2,Gr-3). Lactic acid was added into a medium (Krebs-Henseleit solution) at concentrations of 10.6mM, 15.9mM and 21.2mM for Gr-1, Gr-2 and Gr-3,respectively. After obtaining the constant developed force, concentration of isoproterenol (ISP) in the bath was increased in a stepwise fasion. Developed tension was measured at each concentration of ISP in a steady state. Contractile response to ISP in Gr-c was measured without lactic acid addition. RESULTS By adding lactic acid, medium pH decreased from 7.35 to 7.04 (Gr-1), from 7.35 to 6.80 (Gr-2) and from 7.35 to 6.26 (Gr-3), and developed tension significantly decreased to 72.9±2.4%($p<0.001$), 52.8±2.3%($p<0.001$) and 30.8 ± 4.2% ($p<0.001$:mean±SEM:paired t test) of the initial value in each group, respectively. Under these conditions, ISP produced a sigmoidal increase in contractile force in all groups to concentrations between 5×10^{-9} M and 5×10^{-7} M. Percent increase in maximal developed tension by ISP were 79.6±6.8, 77.6±10.0 ,and 62.5±8.1 in Gr-1,Gr-2 and Gr-3, respectively. None of these values was significantly different from Gr-c (70.5±10.4 : Student t test). CONCLUSION Contractile force of papillary muscle was significantly depressed in lactic acidosis. However, papillary muscle was still able to respond to ISP stimulation. These data may suggest that lactic acidosis does not impair β-receptor-mediated transmission in myocardium.

7 ANTISHOCK ACTIONS OF THYROTROPIN-RELEASING HORMONE (TRH) AND ITS RELATED SUBSTANCE. M. Miyazaki and C. Okuda Kyoto Prefectural Med. College, Kyoto 602, Japan.

Thyrotropin-releasing hormone(TRH) which releases thyroid-stimulating hormone from the anterior lobe of the pituitary was extracted from the hypothalamus and recognized not only as a neurotransmitter but also as a physiological substance to regulate the circulatory system through the central nervous system. The antishock action of TRH is considered antiopioid as naloxone is, but it also antagonizes hypotension induced by leukotriene D4 in which naloxone is inactive. This study shows the mechanism of vasopressor action of TRH and measures TRH content which will show antishock action in rat brain. The fourth ventricle of Wistar male rat was cannulated and the femoral artery and vein were also cannulated for administration of TRH and related substance before the experiment. Blood pressure and pulse rate were measured. TRH content of brain was measured by RIA method after decapitation. Experimental results are as follows:1)Both intravenous and intraventricular administration of TRH and derivative DN-1417(γ-butyrolactone-γ-carbonyl-L-histidyl-L-prolinamide) elevated blood pressure and induced tachycardia for 2 hours with the maximum peak in 1 minute. Effects were blocked by phentolamine, mecamylamine, adrenalectomy and propranolol(in tachycardia). Atropine, a muscarinic cholinergic receptor blocker and haloperidol,a dopamine receptor blocker, suppressed those effects, though bicuculline, a GABA receptor blocker, was not effective. 2)The same effects were noticed in hemorrhagic shock in rat when blood pressure was lowered 40-50 mmHg after exsanguination of 45% of circulatory blood volume. DN-1417 by intraventricular administration expecially showed a long persistent effect. 3)Intracerebral TRH increased with progress of hemorrhagic shock.

8 STEROID HORMONE MODIFICATIONS DURING EXPERIMENTAL AND HUMAN SEPTIC SHOCK. E.A. Nunez*, N. Christeff*, C. Benassayag*, M.C. Auclair*§, A. Carli§§. U. 224, INSERM - Faculté Xavier Bichat, 75018 Paris - § U. 228, INSERM - 15, rue de l'Ecole de Médecine, 75006 Paris - §§ Service de Réanimation Polyvalente, CHU Cochin-Port-Royal, 75674 Paris, FRANCE.

During stress, inflammation and shock the enhanced concentration of glucocorticoids is currently considered to be a moderating factor of the body reactions and an important index for evaluating the severeness of the disease. The other steroids produced by adrenals and other tissues are poorly understood in terms of prognosis and pathophysiological significance. We report here that during human septic shock the serum levels of steroids other than glucocorticosteroids are profoundly different from those of normal men. The levels of estrogens and progesterone were found all higher than in controls ; Δ 4-androstenedione was unchanged while testosterone was lower than normal. The dramatic increase in estrogens (3 to 10 fold) and decrease in testosterone (3 to 11 fold) appear to be correlated with the severity of shock and, so particularly, interesting as a prognostic index in human septic shock. Similar results have been obtained after administration of increasing doses of E. Coli endotoxin to intact male rats. Experiments performed in adrenalectomized or orchidectomized rats indicate that estrogens were largely produced in the testis by aromatization of testicular and adrenal androgens. Pretreatment by indomethacin before endotoxin administration abolished the steroid level modifications observed after administration of endotoxin except for progesterone which level remained significantly higher than in controls.

9 **DOWNREGULATION OF CARDIAC β-ADRENERGIC RECEPTORS IN HEMORRHAGIC SHOCK.** M.Yahagi*, K.Mizumachi*, H.Kawabata*, S.Tezuka*, S.Morita* and K.Okada. Department of Anesthesiology, Teikyo University School of Medicine, 2-11-1 Kaga Itabashi-ku, Tokyo 173, Japan

Alterations in the responsiveness of β-adrenergic stimulation in shock was previously reported. This study was designed to determine whether catecholamine-induced downregulation of β-adrenergic receptors existed in hemorrhagic shock. METHODS Forty male Wistar rats (6-8 weeks old) were divided into 2 groups of 20 rats each. In one group, mean arterial pressure was decreased to 40-50 mmHg by bleeding and kept constant for 6 hours (shock group). The other group served for control. In both groups, the myocardial cell membranes were prepared from whole hearts and assayed for [^{3}H] dihydroalprenolol ([^{3}H]DHA) binding according to the procedure of Mukherjee et al.(J.Clin.Invest. 64:1423,1979). Membranes were incubated at 37°C for 10 minutes with [^{3}H]DHA (0.33-13.3 nM), and then, passed through glass fiber filters. Binding of [^{3}H]DHA to membranes was determined by measuring the radioactivity retained on filters. Specific binding was defined as the difference between the presence and the absence of 10μM dl-propranolol. The maximum number of binding sites (Bmax) and the dissociation constant (K_D) were determined by Scatchard analysis. RESULTS Bmax was significantly decreased by 20 % in the shock group as compared with that in the control group (91.4±5.2 vs. 72.6±3.1 fmol/mg protein in the control and shock group. All values are expressed as mean ± SEM. $P<0.05$ by Student t test). But no significant change occurred in K_D values. CONCLUSION These data suggest that downregulation of cardiac β-adrenergic receptors may account in part for alterations in the responsiveness of cells to catecholamines in shock.

10 LIPID A-INDUCED PROSTACYCLIN PRODUCTION BY CULTURED BOVINE AORTIC ENDOTHELIAL CELLS AND RABBIT HEPATOCYTES. John T. Flynn. Thomas Jefferson Univ., Phila., PA 19107.

Endotoxic shock has been shown to stimulate endogenous eicosanoid production in vivo. The present study was undertaken to determine possible direct effects of lipid A on eicosanoid production in cultured cells. Hepatocytes were isolated from collagen perfused rabbit livers, purified, and cultured for 48 hrs in DMEM prior to use. Bovine aortic endothelial cells were grown in DMEM with growth supplements. Lipid A from E. coli was dissolved in acetone and used at concentrations of 10 and 20 μg/ml of medium. Control group cells received an equal volume of acetone as a vehicle control. Prostacyclin production expressed as nanograms/well over 4 and 24 hr incubation periods for the 2 types of cells was as follows:

	Hepatocytes	Endothelial Cells
Control (4 hr incubation)	0.14±0.02	1.92±0.35
10 μg/ml (4 hr) lipid A	---	3.84±0.49*
20 μg/ml (4 hr) lipid A	0.11±0.01	4.94±0.76*
Control (24 hr incubation)	0.14±0.03	
20 μg/ml (24 hr) lipid A	0.25±0.01*	

*= $p<0.05$ when compared to time and group matched controls. n= 6 to 12.

Thromboxane B_2 production was not stimulated by lipid A in either type of cell. These data demonstrate that bacterial lipid A directly stimulates the arachidonic acid cascade in both hepatocytes and endothelial cells although the rates and magnitude of production differ. This work was supported by GM28023.

11 EVIDENCE AGAINST A ROLE FOR LEUKOTRIENES D4/E4 IN OLEIC ACID INDUCED NON-CARDIOGENIC PULMONARY EDEMA IN THE DOG. H.D. Reines, H. A. Ball, P. V. Halushka
Medical University of South Carolina, Charleston, SC 29425

The potential role of leukotrienes D4/E4 (LTD4/E4) in oleic acid-induced lung injury was investigated in anesthetized dogs by means of a selective LTD4/E4 antagonist, LY171883. Previous studies have demonstrated a three fold use in LTD4/E4 at 60 minutes in bronchial lavage fluid following oleic acid (OA) injection. Methods. Controls (N=5) received saline, Group 2 (n=5) OA (0.06/kg over 15 min) and group 3 (n=7) LY171883 (30 mg/kg) followed in 20 min by oleic acid. Mean arterial pressure (MAP), central venous pressure (CVP), cardiac output (CO), mean pulmonary arterial pressure (MPAP), pulmonary capillary wedge pressure (PCWP), extravascular lung water (EVLW) and arterial blood gases were measured prior to, and 15,30,60, and 120 min following saline or oleic acid. Results. There was no significant change in any parameter in controls. Oleic acid however, decreased MAP significantly from 144 ± 7 mmHg to 98 ± 14 mmHg at 30 min ($p<0.05$). CO, initially 4.1 ± 0.6 L/min also fell to 3.4 ± 0.9. PR, CVP, PCWP and MPAP did not change. EVLW increased from 7.2 ml/kg to 12.2 ± 0.6, 18.2 ± 1.8 and 32.8 ± 2.8 ml/kg at 15,30, and 120 min. Arterial PO2 (FIO2=1.0) fell progressively from 517 ± mmHg to 71 ± 11 mmHg at 120 min. Dogs pretreated with LY171883 failed to show any differences in these parameters compared to those given OA alone. It is concluded that LTD4/E4 receptors, are not responsible for the pulmonary edema following oleic acid injury in the dog.

12 **PROTECTIVE EFFECTS OF A THROMBOXANE (TX) RECEPTOR ANTAGONIST TRANS - 13 - APT ON SPINAL CORD BLOOD FLOW FOLLOWING INJURY.** G. E. Tempel, S. Gianlorenzo*, H. F. Martin*,T. Eller*, D.R. Knapp*, and J. A. Cook. Medical University of South Carolina, Charleston, SC 29425.

PGH_2 / TxA_2, potent vasoactive agents, have been implicated as a mediators of the hemodynamic alterations of circulatory shock. This and reports of progressive ischemia following spinal cord contusion suggested investigation of the role of Tx in the changes in blood flow following spinal cord trauma. Rats were sedated (Ketamine 200 mg/kg) and injected with a Tx synthetase inhibitor Dazoxiben (30 mg/kg), a Tx receptor antagonist APT (30 mg/kg), or vehicle prior to laminectomy (LAM) and standard 24 g-cm injury. Spinal cord blood flow was examined 3 hr post trauma using microspheres.

Treatment	Superior to LAM (ml/min/g)	LAM Area (ml/min/g)
Laminectomy	**0.43 ± 0.14 (12)**	**0.37 ± 0.12 (12)**
Spinal Injury	**0.25 ± 0.9 (9) ***	**0.23 ± 0.10 (9)***
Dazoxiben and Injury	**0.24 ± 0.09 (5)**	**0.20 ± 0.06 (5)**
Trans - 13 APT and Injury	**0.47 ± 0.30 (8) ****	**0.38 ± 0.21 (8) ****

Data are mean ± S.D. of (n) per group. * $p < 0.05$ vs LAM; ** $p < 0.05$ vs untreated and injured.
The nearly 40% decrease in cord flow observed following injury was significantly improved only by pretreatment with a Tx receptor antagonist. The data suggest the involvement of PGH_2 / TxA_2 in cord blood flow changes following trauma. (Supported by NINCDS #2PO1-NS11066-10 and NIH GM 27673.)

13 THE EFFECTS OF CV-3988 AND SRI 63-072 ON PAF INDUCED HYPOTENSION IN DOGS. P. Toth, J. Van Camp*, A. Mikulaschek*, and R. Demeter*. Methodist Hospital of Indiana, Inc., Indianapolis, IN 46202

Prior work has examined the hemodynamic effects of PAF induced hypotension in the dog. The present work examined the effects of two PAF antagonists, CV-3988 and SRI 63-072 on PAF induced hypotension in dogs (18-25 kg). After thiopental anesthesia, impedance cardiography and invasive methods were used to measure various cardiovascular parameters. Hematocrits were also measured throughout each experiment. Animals were treated with either CV-3988 (10 mg/kg), SRI 63-072 (10 mg/kg), or an equal volume of saline 5 minutes prior to the administration of PAF (5.0 ug/kg) (dissolved in 0.25% dog serum albumin) and monitored for 3 hours. Data (mean ± SEM) (normalized to the baseline) measured 2 hours after PAF administration are as follows:

GROUP	MAP (mmHg)	CO (L/min)	TPR (mmHg/L/min)	dP/dt (mmHg/sec)	Hct (%)
CV-3988 (n=7)	- 8 ± 7*	-1.7 ± 0.3	+11 ± 2*	-1432 ± 436*	+12 ± 1*
Saline (n=7)	-89 ± 9	-1.4 ± 0.4	-12 ± 3	-3685 ± 966	+27 ± 1
SRI 63-072 (n=6)	-51 ± 7*	-0.9 ± 0.5	-12 ± 6	-2250 ± 328*	+15 ± 1*
Saline (n=6)	-71 ± 6	-1.0 ± 0.5	- 6 ± 3	-2891 ± 349	+31 ± 1

* $p \leq 0.05$ (compared to control) (repeated measures ANOVA)

These data demonstrate that PAF antagonists can attenuate the effects of PAF. CV-3988 was more potent than SRI 63-072 for attenuating the hemodynamic effects of PAF but both were equally effective on hemoconcentration (Hct).

14 **BENEFICIAL ACTIONS OF DEFIBROTIDE, A PROSTACYCLIN ENHANCING AGENT, IN HEMORRHAGIC SHOCK.** Haim Bitterman*, David J. Lefer* and Allan M. Lefer. Department of Physiology, Jefferson Medical College, Thomas Jefferson University, Philadelphia, PA 19107.

Prostacyclin (PGI_2) is a potent eicosanoid with beneficial effects in ischemia and shock. We studied the effects of defibrotide, a new antithrombotic agent which enhances PGI_2 release from vascular tissue, in rat hemorrhagic shock. Anesthetized rats were bled and maintained at a MABP of 45 mmHg until the rats took back 25% of the bleedout volume, followed by reinfusion of all remaining shed blood. Defibrotide (4 mg/kg) was given as an i.v. bolus at 30 min post-hemorrhage followed by a constant i.v. infusion (4 mg/kg/h). Hemorrhaged rats treated with defibrotide maintained post-reinfusion MABP at significantly higher values compared to rats receiving the vehicle (final MABP, 100 ± 3 vs 69 ± 7 mmHg, $p<0.01$). Defibrotide attenuated the release of the lysosomal hydrolase cathepsin D ($p<0.02$), and the plasma accumulation of free amino-nitrogen groups ($p<0.02$) as well as the plasma activity of myocardial depressant factor (MDF) ($p<0.01$). Additionally, in vitro analysis indicates that defibrotide exerts an antiproteolytic action in pancreatic homogenates, and a lysosomal stabilizing effect in large granule fractions of cat liver homogenates. Moreover, defibrotide enhanced the recovery from norepinephrine induced vasoconstriction in rat aortic rings having an intact endothelium ($p<0.01$ from vehicle), and augmented over two-fold the in vitro release of 6-keto $PGF_{1\alpha}$, the stable metabolite of PGI_2, from rat aorta. Our results indicate that the beneficial actions of defibrotide in hemorrhagic shock are mediated by its effects on vascular PGI_2 release coupled with direct, or PGI_2 mediated, antiproteolytic and membrane stabilizing actions.

15 **ENDOTOXIN TOLERANCE ALTERS HEMODYNAMIC RESPONSES TO U-46619, A THROMBOXANE (Tx) A_2 MIMETIC.** K. A. Coffee*, J. A. Cook, P. V. Halushka, and W. C. Wise. Medical University of S.C., Charleston, SC 29425.

Repeated sublethal doses of endotoxin (LPS) render TOL rats to lethal doses of LPS. Supralethal doses of LPS stimulate TxA_2 synthesis, a pathogenic mediator, in tolerant (TOL) rats to the same extent as that observed in nontolerant (NONTOL) rats, yet TOL rats survive suggesting that LPS tolerance may alter hemodynamic responses to TxA_2. Studies were initiated to assess mean arterial pressure (MAP) responses to iv injections of the TxA_2 mimetic U-46619 at doses ranging from 0.7 to 8.4 μg/kg. NONTOL rats exhibited an initial hypotensive response (15 sec) not seen in TOL rats. Additionally, the maximum pressor response was significantly higher ($p<0.05$) and more sustained at the higher doses in TOL rats compared to NONTOL rats.

ABSOLUTE CHANGE IN MAP (mmHg) AT 15 SEC FOLLOWING U-46619					
DOSE μg/kg	0.7	1.4	2.8	5.6	8.4
NONTOL (n=16)	-1 ± 1	6 ± 1	5 ± 2	1 ± 4	-13 ± 4
TOL (n=15) *	1 ± 1	7 ± 1	10 ± 3	8 ± 2	6 ± 3

TIME RELATED ABSOLUTE CHANGE IN MAP IN RESPONSE TO U-46619 (8.4 μg/kg)					
TIME (SEC)	15	30	45	60	75
NONTOL (n=16)	-13 ± 4	13 ± 3	14 ± 3	7 ± 4	2 ± 4
TOL (n=15) *	6 ± 3	27 ± 3	28 ± 3	24 ± 3	20 ± 3

* $p < 0.05$ by ANOVA. Data expressed as MEAN ± SEM

These results demonstrate that LPS tolerance alters hemodynamic responses to the TxA_2 mimetic, U-46619, which suggest a potential alteration in either Tx receptors or post-receptor coupling events. (Supported by NIH GM-27673 and HL29566).

16 ROLE OF PLATELET-ACTIVATING FACTOR (PAF-ACETHER) IN ACUTE MYOCARDIAL ISCHEMIA IN RATS. Gregory L. Stahl*, Zen-ichi Terashita* and Allan M. Lefer. Department of Physiology, Jefferson Medical College, Thomas Jefferson Univ., Philadelphia, PA 19107.

Infusion of PAF-acether has been shown to exacerbate the extent of cellular damage in the ischemic myocardium. The purpose of this study was to determine if PAF-acether is a mediator of tissue damage in myocardial ischemia (MI). Administration of CV-6209 (1 mg/kg), a new potent PAF-acether antagonist, to sham MI rats had no significant effect on mean arterial blood pressure, heart rate or the pressure-rate index (PRI). Permanent left coronary artery ligation was produced in male rats and ischemic damage was assessed by loss of cathepsin D activity and free amino-nitrogen concentration from the left ventricular free wall (LVFW). Six hours following ligation, there was a significant loss of cathepsin D activity (0.84 ± 0.04 vs 1.67 ± 0.11 IU/mg protein, $P<0.001$) and amino-nitrogen (0.80 ± 0.05 vs 1.12 ± 0.06 U/mg protein, $P<0.01$) from the LVFW in MI compared to sham MI rats. CV-6209 (1 mg/kg) given intravascularly significantly attenuated the loss of cathepsin D (1.07 ± 0.08 IU/mg protein, $P<0.05$ from MI + vehicle rats) and amino-nitrogen (0.98 ± 0.07 U/mg protein, $P<0.05$ from MI + vehicle rats). Furthermore, the cardiac protection appears to be dose-related, as CV-6209 (0.1 mg/kg) only provided slight protection. Moreover, the half-life of CV-6209 was approximately 3 hours, covering the critical time of extension of ischemic damage occurring in this model. These data show that CV-6209 significantly prevents the extension of ischemic damage in the myocardium without exerting any overt hemodynamic effects, indicating that the mechanism of the beneficial effect is via some cytoprotective action. These findings point to an important role of PAF-acether in the pathophysiology of acute myocardial ischemia.

17 THE EFFECT OF SQ 29,548 ON ENDOTOXIN-INDUCED BRONCHOCONSTRICTION IN THE CAT. D. Underwood*, T. Kriseman* and P. Kadowitz* (Spon: J. Spitzer). Tulane University School of Medicine, New Orleans, LA 70112.

Intravenous administration of endotoxin (ENDO), the thromboxane (TX) mimetic drug U46619, and prostaglandin (PG) $F_{2\alpha}$ produced dose-related increases in transpulmonary pressure and lung resistance and a decrease in dynamic compliance in anesthetized, paralyzed, mechanically ventilated cats. The bronchoconstrictor responses to E. coli (055:B5) ENDO (0.75 mg/kg) and U46619 (100 and 300 ng) were reduced by greater than 90% by prior administration of the TX receptor blocker, SQ 29,548 (0.5 mg/kg). Bronchoconstriction due to $PGF_{2\alpha}$ (1 and 3 μg) was not significantly changed by TX receptor blockade. 120 to 180 minutes after administration of SQ 29,548 (0.5 mg/kg) airway responses to U46619 (300 ng) returned to approximately 85% of control level. At this time bronchoconstrictor responses to ENDO returned to near control intensity. Since TX receptor blockade by SQ 29,548 blocked ENDO-induced bronchoconstriction, and since airway responses to ENDO returned concurrently with the return of bronchoconstriction due to U46619, the present data indicate that bronchoconstriction in the closed-chest cat due to ENDO is mediated in large part by the formation and action of TX.

18 SEQUESTRATION OF PLATELETS IN DIFFERENT ORGANS EARLY AND LATE DURING ENDOTOXIN INDUCED SHOCK IN SHEEP. A.A. Al-Sarraf*, A. Owunwanne*, and J.T. Christenson* (Spon: H. Shennib). Department of Surgery and Nuclear Medicine, Kuwait University, Kuwait.

We have studied platelet behaviour in early and late stages of endotoxin induced shock in various organs in a sheep model. Twelve sheep (30-40kg) were anaesthetized and maintained on controlled ventilation. Platelets were harvested and labelled with In-111-oxine and reinj. i.v. Blood pressure was monitored. Blood samples were repeatedly withdrawn for platelet and activity counting. Gamma camera images of head and chest/abdomen were obtained continously until the death of the animal. Endotoxic shock was induced by a slow i.v. E. Coli endotoxin injection (3mg/kg). Platelet activity in lungs, liver, spleen, kidney, brain and carotid artery were analyzed from computer images at different times. All animals died within 8 hours. Platelet and activity counts showed a sharp drop ($p < 0.001$) 5 min after inj followed by recovery (at 1 hr), then gradual decrease. Platelet activity in the brain did not change during the first 2 hours. Lung, liver and kidney activities increased significantly during the first 20 min, followed by a decrease in activity, then a second increase at 1.5 hr after inj. After a second activity drop, lung activity stayed stable up to 1 hr prior to death when again an increase was noted. Liver and kidney activity had a final decrease. Spleen activity showed decrease 20 min after inj, stayed low until 2 hr prior to death when it increased. Early platelet trapping occurs, in lung, liver and kidneys, followed by disaggregation without accumulation in the spleen. A second and third wave of platelet aggregation occured in these organs. No platelet accumulation or trapping was seen in the brain.

19 COMPARISON OF PLATELET-ACTIVATING FACTOR AND E. COLI ENDOTOXIN INFUSION IN RABBITS. Arthur Prancan*, Renlin Xia*, and Marguerite Littleton*(Spon: Linda T. Archer.) Department of Pharmacology, Rush Medical College, Chicago, IL 60612 USA.

Platelet-activating factor(PAF) can cause biological responses which are also seen as manifestations of endotoxin during shock. Therefore, we compared the effects of PAF and E. coli endotoxin on hemodynamics, blood cell counts, prostacyclin and thromboxane in rabbits. PAF(100 ng/kg/min) and E. coli endotoxin(20 ug/kg/min, LD67) were infused via the R jugular vein for 120 min in separate groups. PAF(N=6) thrombocytopenia was seen within 5 min. of infusion(33% of control counts). WBC values decreased from 3,917/mm^3 to 1,500/mm^3 by 30 min. Diastolic blood pressure remained stable at preinfusion values(78 mmHg) until 30 min. (63 mmHg) and then dropped to 41 mmHg by 120 min. Heart rate was unchanged, or increased as diastolic pressure fell. Prostacyclin (6-keto-PGF_{1a}, RIA) arterial values were at control levels for 15 min., reached 234% at 30 min. and continued to 605% by 90 min. Thromboxane(TXB_2, RIA) arterial values also rose above control between 5 and 15 min. in a preliminary trial. Endotoxin(N=5) infusion produced similar changes in these parameters. Platelet counts dropped to 43% of control by 15 min. WBC were at 34% of control by 30 min. Diastolic blood pressure dropped from 79 mmHg to 64 mmHg between 60 and 90 min and reached 58 mmHg at 120 min. Prostacyclin rose above control(30 min.) to 2,200% of control at 120 min. TXB_2 reached the peak blood level within 30 min. The parallel between PAF and E. coli endotoxin actions on these parameters suggests that PAF may be an important mediator of endotoxin shock. Supported by Chicago Community Trust and Sigma Xi.

20 INTUSSUSCEPTIONS, THE OVERLOOKED LESIONS OF ENDOTOXIC OR SEPTIC SHOCK. L.T. Archer, J.V. Pitha*, R. Ochoa, and L.B. Hinshaw. VA Med. Ctr. and University of Okla. Health Sci. Ctr, OKC, OK 73104 and The Upjohn Company, Kalamazoo, MI 49001.

Multiple pathologic changes result from endotoxic/septic shock including: congestion, edema, hemorrhage, and/or necrosis of adrenal glands, liver, kidneys, lungs, and intestinal tract. We recently conducted 15 therapy studies in dogs and baboons (N=268) subjected to endotoxic or live E.coli-induced shock to determine the effect of each specific therapy on different endpoints: in 10 studies/permanent survival (>7 days) and in 5 studies/pathophysiologic mechanisms. As a routine part of each study, we performed autopsies on each animal. We observed intestinal intussusceptions (ints) that to our knowledge have not been observed or reported as a result of endotoxic/septic shock. The lesion involves the slipping of one section of an intestine into another part distal to it. We documented ints in 49 of 268 or 18% of the animals. The lesions ranged from 2.5 - 45 cm,

were mainly enteric, and in one instance was a total, ileocecal intussusception. In another animal 9 lesions involving virtually all of the jejunum and ileum were observed. In the 10 permanent survival studies this lesion was observed in 21% of the nonsurviving animals. Ints were observed in 25% of the animals in the 5 remaining studies. Animals with ints died between 12 - 456 h after the onset of E. coli or endotoxin. Five animals with ints survived the initial shock (>7 days). Three were euthanized between 7 - 9 days (their lesions would have eventually caused death) and 2 died at 14 and 19 days respectively. This lesion although unreported in shock studies no doubt contributes to the lethality of shock.

21 IMPAIRED HEPATIC ENERGY PRODUCTION DURING SEPTIC SHOCK. M. Astiz,* E.C. Rackow, M.H. Weil, W. Schumer. UHS/The Chicago Medical School, North Chicago, IL 60064.

Energy production was studied during murine peritonitis. Septic shock was produced in Sprague-Dawley rats by cecal ligation and perforation. Polymicrobial bacteremia was documented by blood culture. Thermodilution cardiac output (CO), and arterial lactate were measured prior to and sequentially after cecal perforation. At 6 h, the liver was biopsied to assay lactate, pyruvate and adenine nucleotides. Hepatic energy charge was calculated as ATP + 1/2 ADP/ATP + ADP + AMP. The study included 5 sham rats (SH), 5 septic rats and 5 septic rats infused with 5% albumin (SA) in amounts which maintained central venous pressure at baseline level. Data at 6 h are presented as mean ± SE (N), *p < 0.05 S vs SH, †p < 0.05 SA vs SH.

	SH (5)	S (5)	SA (5)
CO ml/kg/min	310 ± 25	172 ± 9*	419 ± 48
Lactate mmol/l	0.8 ± 0.6	2.1 ± .23*	0.8 ± 0.5
Lactate/pyruvate	10.5 ± 0.8	16.2 ± 1.0*	14.3 ± 0.8†
ATP mmol/g	3.26 ± 0.06 (4)	2.51 ± .12*	2.96 ± 0.05 (4)†
Energy charge	.831 ± .01 (3)	.771 ± .01*	.814 ± 0.01 (3)

Despite the maintenance of CO in SA rats, increase in hepatic lactate/pyruvate ratio and decrease in hepatic ATP and energy charge was observed. These data suggest that impaired cellular oxidative metabolism and energy production occurs early in the course of sepsis and shock.

22 EXPERIMENTAL STUDY OF ENDOGENOUS ENDOTOXEMIA

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Three absorption routes of endotoxin derived from the intestine of shocked rabbits, namely via portal vein, via intestinal lymphatics and via transperitoneal routes have been studied. As the intestinal circulatory disorders, superior mesenteric artery occlusion (SMAO) and superior mesenteric vein occlusion (SMVO) were induced. Furthermore, in order to investigate the transperitoneal route, fecal peritonitis was induced. Detection and quantitation of endogenous endotoxin in plasma and lymph were carried out using synthetic chromogenic substrate, peptide-4-methylcoumarin amide (MCA). In the SMAO group, endotoxin levels in portal plasma exceeded levels in lymph from the thracic duct throughout the experiment, and in the SMVO group, the relationship was reversed. In peripheral arterial blood, endotoxin levels were significantly lower in rabbits with thoracic duct lymph drainage than in those with intact lymphatic system. In rabbits with fecal peritonitis, endotoxin levels in lymph form the thoracic duct exceeded levels in portal plasma throughout the experiment. Based on the results described above, intestinal lymphatics was expected to play more important role than the other routes in systemic endotoxemia in non-septic shock.

23 THE EFFECTS OF ENDOTOXIN SHOCK ON SPLANCHNIC VENOUS COMPLIANCE. R. R. Beck* and E. L. Abel. University of South Carolina Sch. Med., Columbia, SC 29208.

We have previously demonstrated that endotoxin shock is associated with a decrease in compliance of the superior and inferior vena cavae and probably

central pooling of venous blood. These studies were designed to investigate the influence of endotoxin on compliance of the venous bed drained by the portal vein. A flow probe was placed around the superior mesenteric artery and a catheter was inserted into the portal vein. The spleen was removed and the inferior mesenteric artery, left gastric, and splenic branches of the celiac axis tied. Flow was measured in the mesenteric artery while the portal vein was occluded. The rate of rise of pressure in the portal vein was compared with the inflow to the venous system. Compliance was measured during a 30 min. control period, for 1 hr. after 0.5 mg/kg of E. coli endotoxin, and for 1 hr. after treatment with 10 mg/kg ibuprofen. Endotoxin caused an increase in venous compliance; this increase was reversed by ibuprofen. Arterial resistance in this bed decreased slightly after endotoxin, but increased above control levels after ibuprofen. We interpret the increase in venous compliance to indicate venoconstriction of the splanchnic bed. Thus, there is venous constriction but not arterial constriction of the splanchnic bed following endotoxin. Treatment with ibuprofen restored the venous compliance to normal, representing an accompanying decrease in venous constriction but flow remained low despite restoration of arterial pressure, representing arterial constriction. Supported by grants from S.C. Heart Association and Upjohn Company.

24 INTERACTIONS BETWEEN ENDOTOXIN, THE LIVER, SYSTEMIC HEMODYNAMICS AND AMINO ACID METABOLISM. W. Becker*, F. Konstantinides* and F. Cerra. Department of Surgery, University of Minnesota, Minneapolis, MN 55455 and Department of Surgery, William Beaumont Army Medical Center, El Paso, TX 79920.

This study evaluated the interaction between the liver, systemic hemodynamics and amino acid metabolism during E coli endotoxemia. Twelve (12) adult mongrel dogs were divided into four groups. All animals underwent side to side portal-caval shunt (PCS), three only had PCS, three underwent PCS and received E coli endotoxin (LPS), 0.5 mg/kg/hr for two hours, three had PCS and total hepatectomy with vena cava reconstruction (PCS +H) and three had PCS + hepatectomy + endotoxin infusion (PLS +H+LPS). All animals received similar volumes of saline. Mean arterial pressure, CVP, cardiac output (CO) and total and individual plasma amino acid clearance (PAAC) were measured following bolus amino acid injection. Administration of LPS resulted in a hyperdynamic state with increased CO and decreased total peripheral resistance (TPR) irrespective of hepatectomy (CO 2.0 $\pm$ .2, TPR 3650 $\pm$ 305 Pre LPS; CO 4.9 $\pm$ .4, TPR 1105 $\pm$ 98 post LPS, $P < .05$). Animals not receiving LPS did not have a significant change in hemodynamics. PAAC was significantly depressed in animals undergoing hepatectomy (480 $\pm$ 96 ml/min prehepatectomy, 78 $\pm$ 38 ml/min, post hepatectomy, $P < .05$). Administration of LPS alone also significantly decreased PAAC (390 $\pm$ 76 to 110 $\pm$ 33, $P < .05$), despite increasing CO. We conclude that LPS administration causes a hyperdynamic state independently of hepatic factors and also markedly decreased amino acid clearance.

25 GROUP B STREPTOCOCCAL SEPSIS IN THE PIGLET: EFFECTS OF FLUID THERAPY ON VENOUS RETURN AND ORGAN EDEMA.

M. A. Bressack*, N. S. Morton*, J. Hortop*. McGill Univ., Montreal, Que. H3H1P3.

We investigated the differential effects, over 4 hours, of saline versus 5% albuminated saline fluid resuscitation on cardiovascular function and organ edema in 10-12 day old piglets infected with intravenous group B streptococci (1×10^{10}/kg); enough intravenous fluid (IF) was given to maintain baseline cardiac output. N = 10 in all groups. Measured values included cardiac index (CI), right and left atrial pressure (Pa), mean circulatory pressure (Pmc) plasma protein oncotic pressure (πmv), blood volume (V), and organ edema (wet/dry weight ratio). Summary of results after 4 hours, *significant difference ($p<.05$) compared to control group:

	CI l/m•kg	Pra torr	Pla torr	Pmc torr	πmv cmH$_2$O	V ml/kg	IF ml/kg
Control	.23±.02	3.6±0.9	4.0±1.1	7.1±0.9	15.5±1.2	78+4	-
Untreated	.12±.04*	0.9±0.9*	1.3±0.8*	6.9±0.9	13.6±1.6	71+4*	-
Saline	.22±.05	4.1±2.0	4.8±3.0	10.2±2.0*	10.0±1.6*	87+4*	155±45*
Albumin	.23±.05	4.0±1.8	4.7±2.0	10.8±1.1*	18.2±1.4*	90+6*	58±13*

Resistance to venous blood return nearly quadrupled in the untreated group as shown by a 50% decrease in CI with a nearly doubling of driving pressure for venous return (Pmc-Pa). In both fluid-treated groups resistance doubled as shown by an unchanged CI with a doubling of driving pressure. Organ edema (ileum, pancreas, kidney, adrenal, lung) occurred only in the saline-treated group, associated with a 50% increase in Pmc and a 36% decrease in πmv.

26 MOLECULAR PROPERTIES OF ALTERED ALPHA1-ADRENERGIC RECEPTORS IN RAT INTRAPERITONEAL SEPSIS. Joe A.Carcillo*, Josephine Lai*, J.Craig Venter*, and Bryan L. Roth, Surgical Res. Branch, Naval Med. Rsch. Inst. Bethesda,MD 20814-5055, and Section of Receptor Biochem., NIH, Bethesda, MD 20814.

We previously demonstrated (McMillan et al, Circ Shock, 1986) significant alterations of hepatic alpha1-adrenergic receptors in rat intraperitoneal sepsis. We now report on the molecular properties of these altered receptors as well as provide data which shows that vascular alpha1-adrenoceptors are also altered in intraperitoneal sepsis. Following cecal ligation and puncture, hepatic and aortic plasma membranes were purified by differential centrifugation and Percoll gradients. Hepatic alpha1-adrenoceptors were cross-linked with [3H]-phenoxybenzamine, solubilized in sodium dodecyl sulfate (SDS) and run on polyacrylamide gels (PAGE) as previously described (Venter, et al, Proc. Natl. Acad. Sci.,1986). Aortic receptors were labelled with [3H]-prazosin and analyzed by non-linear least squares regression analysis. Three peaks of activity were found by SDS-PAGE: *146,000, 76,000 and 56,000 daltons*. All three peaks were decreased by 30-50% indicating that the decrease in receptor number was not due to proteolytic degradation of the receptors. Further, a 50% decrease in aortic receptors was documented ($p < 0.01$). These results demonstrate that down-regulation of receptors occurs in the absence of proteolysis in liver and vascular tissue. Supported by MR 04120.05.

27 **IS MYOCARDIAL ADRENERGIC RESPONSIVENESS BLUNTED BY THE LIPID SOLUBLE CARDIODEPRESSANT FACTOR (CDF) IN ENDOTOXIN RATS ?** **A. Carli, C. Gardey*, G. Thiroux* and G. Olive*.** Réanimation Médicale and Labo. Pharmacologie Biochimique. C.H.U. Cochin-Port-Royal, PARIS, F-75674, France.

A sublethal nonhypotensive i.v. dose (2mg/kg) of E. coli endotoxin (ET) in the rat has previously been found to induce the early (from hr 1) and long-lasting (beyond hr 16) release of a lipid soluble CDF reducing cultured rat heart cell response to isoproterenol (ISO) (Circ Shock 8:301,1981). In the present study, Wistar rats were saline or ET (2 mg/kg i.v.) injected and sacrificed 4 hrs later after light chloralhydrate anesthesia. The hearts were removed and ventricules were kept, freezed, and weighed. Ventricular membranes were immediately prepared as HANCOCK et al. (Mol Pharmacol 16:1,1979). The final pellets were resuspended in smaller volume of sucrose/histidine buffer and stored at -80°C. The binding study of β-adrenoceptors was performed with 3H-dihydroalprenolol using d-l-propranolol to determine non specific binding. It has been evidenced no significant difference in adrenoceptor density between control and ET-treated preparations. Adenylate cyclase assay was carried out with crude membrane suspension diluted from 48000g centrifugation pellet. Basal, ISO-, fluoride-, and Gpp(NH)p-stimulated adenylate cyclase activities were not affected. We conclude that in our experimental conditions, the myocardial β-adrenoceptor adenylate cyclase complex is not altered in vivo, despite the prolonged presence of the circulating cardiodepressant factor. Thus, effect of the latter on ISO response could be mainly related to a calcium dysregulation into the cell, as previously suggested (Adv Shock Res 10:161,1983).

28 QUANTITATIVE ULTRASTRUCTURE OF SKELETAL MUSCLE IN HYPERDYNAMIC SEPSIS. R.S. Connell, M.W. Harrison, L. Mela-Riker, D. Trune, R. Bryant, P. Alexander, D. Luallin L. Widener & J. Gellatly, Oregon Health Sciences University, Portland, OR

Chronically catheterized rats were made septic by inoculations of E. coli B. fragilis and S. aureus into a preformed subcutaneous abscess. All septic animals had intermittent E. coli bacteremia and significantly increased white cell counts (from control of $18.8+6x10^3$ to $31.6+4x10^3$), and decreased muscle mass and body weight in spite of normal or increased food and water intake. Cardiac output, measured by thermodilution, increased to a mean of 300% of control. After 3-14 days of sepsis the rats were killed and skeletal muscle collected for a quantitative ultrastructural analysis. Control animals were catheterized and had noninfected abscesses. The following results were obtained:

	Myofibrillar area (μm^2) (S.E.)	Mitochondrial area (μm^2) (S.E.)	Glycogen particles/μm^2 Perimyofibrillar	Perimitochondrial
Control	1.24 (0.073)	0.187 (0.009)	0.37	1.27
Experimental	0.64 (0.026)	0.276 (0.017)	9.13	6.73
	$p<0.005$	$p<0.005$	$p<0.005$	$p<0.05$

The decrease in myofibrillar cross sectional area and the increase in size of mitochondria and numbers of glycogen particles support the hypothesis that parallel with increased skeletal muscle protein catabolism, there is a decreased utilization of available glycogen in the hypermetabolic septic state. Grants from NIH (GM33267) and ONR.

29 DOSE DEPENDENT HEMODYNAMIC RESPONSE TO LIVE PSEUDOMONAS IN SHEEP. D. Dehring, D. Traber, R. Fader*, L. Traber*, S. Doty*. U Tx Med Branch, Shriners Burns Inst, Galveston, TX 77550. (Sponsored by HL 36288-01A1, SBI 86-03-101).

Sepsis results in hyper or hypodynamic circulation. Three groups of sheep (n=8) were infused with 3 doses of bacteria to see if hemodynamic patterns correlate with amount. After insertion of chronic Swan-Ganz & aortic catheters & while receiving maintenance fluid, live Ps. aeruginosa were infused for 1 hr: LO=$1x10^7$; MID=$5x10^7$; & HI=$2.5x10^8$ Ps/min. Pulmonary hypertension was proportional to Ps. given. In LO systemic vascular resistance (SVR) decreased and cardiac output (CO) increased at 8 hr. MID was hyperdynamic at 6-12 hr with increased CO & decreased mean arterial pressure (MAP) & SVR. HI was hypodynamic at 4-8 hr with 3 deaths. At 18-24 hrs HI was hyperdynamic. The dose dependent hemodynamic responses to Ps. produced the clinical patterns seen with sepsis.

		0	4	8	24 hr
MAP	LO	92±4	101±4	92±4	87±5
mm	MIC	96±4	101±3	$82±3^{x*}$	$85±3^{x}$
Hg	HI	99±3	98±6	$76±4^{x*}$	$81±7^{x}$
CO	LO	5.7±0.5	5.5±0.4	$7.1±0.3^{x}$	5.7±0.5
L/	MID	6.6±0.4	5.8±0.5	$8.5±0.3^{x*}$	$7.0±0.4^{x*}$
min	HI	5.9±0.4	$4.6±0.4^{x}$	$4.6±0.5^{x*}$	$8.6±1.0^{x*}$
SVR	LO	1351±99	1515±109	$1066±82^{x}$	1274±101
dynes	MID	1272±98	1565±147	$833±72^{x*}$	$1052±82^{x}$
sec cm^{-5}	HI	1463±144	$1809±197^{x}$	1503±174*	$838±117^{x*}$

x = $p < 0.05$ within groups * = $p \leq$ LO vs MID & HI

30 ANTIBODIES DIRECTED AGAINST GRAM NEGATIVE LIPOPOLYSACCHARIDES AND CORE MOIETTES IN NORMAL BLOOD DONORS AND HOSPITALIZED PATIENTS. J.E. Doran, E. Ehrengruber*, M. Monteil*, H.-B. Ris*. Dept. Experimental Surgery, University of Berne Hospital, Bern, Switzerland.

The importance of antibodies in the control of gram-negative infection and shock has been discussed by a number of authors. Although antibodies in general are considered to be important, the spectrum of antibody reactivities to bacterial lipopolysaccharides has not been defined in the normal populati ing judgement of the relative importance of various antibody classes in the c lly ill patient more difficult. We have utilized ELISA technology to measure b IgG and IgM antibody activities directed against smooth lipopolysaccharides (intact endotoxins) and against the core region (Lipid A) of Salmonella Re595. In addition, total IgG and IgM levels were also assessed. In our population of normal donors (n=229), total IgG correlated highly with total IgM ($p < 0.001$), and with IgG antibodies against Lipid A ($p< 0.05$) but not with IgG antibodies against intact endotoxins. Total IgM

levels correlated with IgM reactivity against both intact endotoxin and Lipid A. However, IgG levels against Lipid A showed no association with IgG levels against intact endotoxins. Hospitalized surgical and intensive care patients were found to have lower levels of total IgG and IgM antibodies, and lower levels of IgM reactive with endotoxin than did the normal population, yet did not differ with respect to IgG reactivities against endotoxin. Due to the wide variability of antibody reactivities seen in the normal population, low levels of anti-core or anti-endotoxin antibodies in clinical practice have only limited prognostic value.

31 EFFECT OF DILTIAZEM ON CELLULAR CALCIUM ALTERATIONS IN SKELETAL MUSCLE DURING ENDOTOXIC SHOCK. K.M. Dudley*, S.R. Maitra* and M.M. Sayeed. Dept. of Physiology, Loyola University Stritch Sch. of Medicine, Maywood, IL 60153.

Cellular Ca^{2+} overload has been implicated in ischemia. This study evaluated whether there is an increase in intracellular Ca^{2+} in the skeletal muscle of endotoxic animals. Additionally, the efficacy of the Ca^{2+} antagonist diltiazem in abrogating cellular Ca^{2+} overload was examined. Rats were given intravenous injections of saline (control), S. enteritidis endotoxin (40 mg/kg) (ETX) or endotoxin (40 mg/kg) plus diltiazem (1 mg/kg) (ETX + DZ). They were killed 5 hours later at which time endotoxic rats showed signs of shock. Soleus muscles were labeled with ^{45}Ca and the radioactivity sequentially washed out to determine intracellular exchangeable Ca^{2+} pool sizes. Plasma glucose levels were 108 ± 4 mg/dl (mean ± SE) in controls, 56 ± 8 in the ETX group, and 68 ± 9 in ETX + DZ animals. Plasma lactates were 1.5 ± .06 mmol/L, 4.9 ± .6, and 4.3 ± .7 in control, ETX, and ETX + DZ rats respectively. Exchangeable intracellular Ca^{2+} appeared higher in ETX animals (1.42 μmol/g, n = 10) than in controls (1.18, n = 14). Exchangeable intracellular Ca^{2+} in ETX + DZ group (1.16, n = 18) was comparable to that found in controls. These data support the concept that endotoxic shock causes elevation of intracellular Ca^{2+} which can be attenuated after treatment of endotoxic animals with diltiazem. (Supported by NIH Grants GM32288 & HL31163).

32 THE INFLUENCE OF HEPATIC CARBOHYDRATE METABOLISM IN RAT PERITONITIS SEPTIC SHOCK T. Ebata, H. Minamida, K. Azuma, H. Hayasaka, R. E. Kuttner and W. Schumer Departments of Surgery, Sapporo Medical College, Sapporo, Japan and University of Health Sciences/The Chicago Medical School, N. Chicago. IL, 60064

In septic shock, accelerated glycolysis occurs and may either be associated with rapid glycogen mobilization or with compensatory changes in glucoregulatory enzymes. This possibility was investigated using glucoregulatory enzymes and TCA cycle activity of liver slices from fasted rats after inducing peritonitis by cecal incision. Liver samples were taken at 3 and 5h. These samples free of mitochondria were assayed by UV spectrophotometry for phosphofructokinase (PFKase), pyruvatekinase (PKase), glucose-6-phosphatase (G6Pase), fructose-1.6-diphosphatase(FDPase), and phosphoenolpyruvate carboxykinase (PEPCK). The liver slices held medium solution plus ^{14}C-glucose, ^{14}C-glutamate or ^{14}C-pyruvate and were gassed with 95% O_2-5% CO_2 gas mixture. The reaction allowed to continue for two hours. Incorporation rate was calculated from the formula. Although at 5h septic PFKase was 22.3±2.9 U/g protein/min and PKase was 252±32, these enzymes were significantly stimulated 13% and 14% respectively. No other differences were noted. The rate of TCA cycle activity was significantly decreased 55% in the septic 5h group. Thus an increase in glycolysis was a common finding in septic shock and was an apparent compensatory reaction for diminished mitochondrial TCA cycle function.

33 FUNCTIONAL ACTIVITY OF ANTITHROMBIN-III IS REQUIRED FOR PROTECTION IN THE E. COLI ENDOTOXEMIC RAT. Thomas E. Emerson, Jr., Robert E. Jordan*, Thomas B. Redens* and Michael A. Fournel*. Cutter Group of Miles Laboratories, Inc., Berkeley, CA 94710.

We have previously reported that pretreatment with functionally active human antithrombin-III (AT-III), a major inhibitor of coagulation enzymes, markedly

increases survival in the E. coli endotoxemic rat model. Specifically, survival in 124 rats pretreatment with 250 U/kg AT-III was 80% compared to 32% in paired saline control rats, a highly significant difference ($P<0.005$). Also, disseminated intravascular coagulation was significantly attenuated in endotoxemic rats pretreated with functionally active AT-III ($P<0.05$). The present preliminary study was completed to confirm that the inhibitor function of AT-III is required for its protective effect. Purified human AT-III was proteolytically inactivated by incubation with human sputum elastase; after isolation from the incubation mixture, less than 1% functional activity remained while full antigenic identity was maintained. Sprague-Dawley rats (350-500 gms) were injected ip with 250 U/kg inactivated AT-III (n=20) or an equal volume of normal saline (n=20) immediately prior to ip injection of 5 mg/kg E. coli endotoxin. Survival was monitored for 7 days. There was no significant difference in survival between the group treated with inactivated AT-III and the group treated with normal saline ($P>0.05$). Thus, pretreatment of endotoxemic rats with inactivated AT-III is not protective whereas pretreatment with functional active AT-III markedly increases survival. Results of the present study suggest that the protective effect of AT-III is due to its ability to function as an inhibitor of coagulation enzymes.

34 ENDOTOXIN BLUNTS THE CHRONOTROPIC RESPONSE TO ISOPROTERENOL IN THE DOG MODEL. D.R. Gentili*, T.J. Iberti, S.R. Berger*, T.A. Paluch*, E. Benjamin. Departments of Surgery & Anesthesiology, The Mount Sinai Medical Center, New York, N.Y. 10029.

Previous studies have demonstrated myocardial depression associated with endotoxemia. In addition, we recently described a significantly slower heart rate (HR) seen in canine endotoxic shock than that observed with hemorrhagic shock of similar severity. The purpose of this study was to examine the chronotropic effects of isoproterenol (ISO) in endotoxic dogs to determine if the negative chronotropy seen in endotoxemia could be eliminated by beta agonist therapy. Eighteen dogs were anesthetized, ventilated and hemodynamically monitored. After stabilization, they were randomized to 3 groups. Group I received isoproterenol 0.1 mg/kg/min; Group II 4 mg/kg E. coli endotoxin (ENDO); and Group III received both ISO and ENDO.

	HEART RATE (± SD)	BASELINE	Rx
I	(ISO)	150 ± 27	201 ± 18 ($p<0.05$ vs. Control, II, III)
II	(ENDO)	158 ± 13	120 ± 15 ($p<0.05$ vs. Control, I, III)
III	(ISO + ENDO)	161 ± 26	140 ± 21 ($p<0.05$ vs. Control, I, II)

The results of this study demonstrate that the chronotropic effects of ISO are depressed in the presence of endotoxin. Thus, in the endotoxic animal model, beta adrenergic stimuli does not overcome the negative chronotropic response to endotoxin. The pathophysiology of this phenomenon remains to be defined, but may involve nodal ischemia, diffuse myocardial depression, or direct action of endotoxin.

35 PLASMA HISTAMINE CONCENTRATIONS DURING ENDOTOXEMIA. DJ Brackett, SA Hamburger, MR Lerner*, TJ Lander*, CF Schaefer, DP Henry*, and MF Wilson. VA Medical Center and University of Oklahoma Health Sciences Center, Oklahoma City, OK, 73104; Indiana University School of Medicine, Indianapolis, IN 46202.

This study was designed to measure plasma histamine (H) concentrations in conscious, instrumented rats challenged with LD_{90} endotoxin (E) using a highly sensitive and specific radioenzymatic assay (REA). Fifteen rats were instrumented for cardiovascular measurements. Cardiovascular parameters for the control (C) rats (7) were stable throughout the 4.5 hr study. Rats given E (8) had typical responses for this model: an early 30 min hypotension episode, decreased cardiac output and central venous pressure, and increased systemic vascular resistance and heart rate. Arterial blood samples were taken before saline or E (40 mg/kg i.v.) and 5, 30, 60, and 240 min after intervention for plasma H determinations using an REA with a sensitivity of 0.84 pg. H values for the C vs the E groups at the designated times were: pre, 9.6 ± .8 vs 9.4 ± 1.0; 5 m, 7.0 ± .8 vs 8.1 ± 1.7; 30 m, 7.7 ± .6 vs 11.0 ± 1.8; 60 m, 7.7 ± .5 vs 15.8 ± 2.3; and 240 m, 8.1 ± 1.1 vs 26.3 ± 7.5 ng/ml. E induced a significant increase at 60 and 240 and was not associated with the early

hypotensive episode. Three rats that died before 240 min had final concentrations of 91, 42, and 174 ng/ml and were not included in the 240 min mean. Contrary to earlier reports using less sensitive or specific assays, these data indicate that the plasma H level is not elevated at the nadir of the hypotensive episode following E, increases significantly beginning at 60 min, and is highly elevated just prior to death. Funding: AHA Fellowship Grant, Ind. Affiliate, and VA Medical Res. Funds.

36 DOSE EFFECTS OF THE HISTAMINE H_1 AND H_2 RECEPTOR ANTAGONIST SK&F 93319 ON CARDIOVASCULAR DETERIORATION DURING CIRCULATORY SHOCK. Michael F. Wilson, Megan R. Lerner*, Theresa J. Lander*, Carl F. Schaefer, Bjorn Biber, Lennart Fagraeus, and Daniel J. Brackett. VA Medical Center and Departments of Medicine and Anesthesiology, University of Oklahoma HSC, Oklahoma City, OK.

The role of histamine in the progression of circulatory shock has not been settled. We have evaluated the dose effect of a histamine antagonist (HA) that acts at the H_1 and H_2 receptors on the development of shock induced by endotoxin (40 mg/kg)(E). Conscious rats (45) in 5 groups were instrumented for measurement of cardiac output (CO), aortic blood pressure, and heart rate. Measurements were made for 4 hrs after induction of shock and arterial blood (200 ul) was taken at control and 1 and 4 hrs for measurement of lactate (L), glucose (G), hematocrit (H), pH, PCO_2, and PO_2 to assess metabolic function. Saline or 10, 20, 70, or 100 mg/kg of the HA (300 ul) was given i.v. 10 min prior to E. The 70 and 100 mg/kg doses, but not 10 and 20 mg/kg, proved to be significant interventions supporting CO and attenuating the sustained increase in systemic vascular resistance. Both high doses also ameliorated the typical deterioration of pH, PO_2, PCO_2 and G found in shock. Only the 100 mg/kg significantly improved L and H responses. SK&F 93319 administered at high doses can produce a substantial attenuation of cardiovascular deterioration and metabolic dysfunction during circulatory shock.
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37 APROTININ INHIBITS THE CARDIOPULMONARY RESPONSE TO ENDOTOXIN IN SHEEP. D. Traber, G. Schlag, D. Herndon, H. Redl*, L. Traber*. Ludwig Boltzman Inst of Traumatology, Vienna, Austria, and UT Med Br and Shriners Brns Inst, Galveston, TX, 77550.

Endotoxin (LPS), as a continuous infusion of 12 ng/Kg/hr, produces a cardiopulmonary response characterized by an increased lung lymph flow (LQ) and cardiac output (CO), and reduced total peripheral vascular resistance. This response is associated with a fall in prekallikrien (PKK) levels, evidence of activation of the kallikrien bradykinin system. We tested the effects of the proteolytic enzyme inhibitor, aprotinin, a drug which blocks PKK activation on the response to LPS. METHODS: Cardiopulmonary variables were measured in sheep which had been chronically prepared for study, 7 days previously. An infusion of aprotinin was then begun. The infusion rate was 10,000 u/Kg which was started after an initial bolus of 20,000 u/Kg. An infusion of LPS was administered at a rate of 12 ng/Kg/hr 2 hrs later. The response of the animals was compared to another group treated in the same manner, but without of aprotinin. RESULTS: A typical response to continuous infusion of LPS was noted in the untreated group. There was a 3X increase in LQ and CO increased by over 1 l/min. The administration of aprotinin resulted in an almost complete blockage of this response. CONCLUSION: The fact the cardiopulmonary response to LPS occurs in association with the activation of the kallikrien bradykinin system and this response is inhibited by the aprotinin, a drug which blocks the kallikrien bradykinin system, is strong evidence that both the microvascular permeability increases and elevation in CO are mediated by a product released by this cascade, perhaps, the peptide, bradykinin.

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38 TEMPORAL PATTERN OF B_1 ADRENORECEPTOR DOWN-REGULATION IN AN ANIMAL MODEL OF NORMOTENSIVE SEPSIS. Suzanne Cadden*, Richard Philp*, William Sibbald. University of Western Ontario, London, Ontario, Canada N6A 5A5.

Systemic sepsis may be associated with adrenoreceptor dysfunction. We therefore analyzed B_1 adrenoreceptor number (BAR) in the myocardium of rats subjected to intraperitoneal sepsis by cecal ligation and puncture. BAR number was quantitated by [H^3]-dihydroalprenolol binding in left ventricular membrane preparations at 12, 16, 20 and 24 hours following peritoneal contamination. Mean arterial BP was constant through all study periods. BAR number was depressed only at 24 hours following peritoneal contamination [Control (n=9), 44.6±1.7; Septic (n=8), 30.8±2.8 fmol/mg protein; P<.05]; this was concurrently associated with depressed contractile tension of isolated papillary muscle [Control (n=5), 3.35±0.2; Septic (n=5), 2.06±0.12 gm/mm²; P<.01]. The reduction in BAR number preceded any decline in mean BP, although both an increased lactate and depressed serum glucose were noted before the decline in BAR number. Changes in BAR number were not related to arterial pH. We conclude that depressed BAR number in this normotensive septic model was responsible for depressed myocardial performance, but that changes in BAR number seem to occur late in the septic process and are not explained by either the effects of an acidosis or systemic hypotension.

Grant Support: Ontario Heart Foundation

39 THE EFFECT OF PERITONITIS ON MYOCARDIAL INSULIN RESPONSIVENESS IN THE CONSCIOUS DOG. J. Dietrick* and R.M. Raymond Depts. of Surgery and Physiology, Loyola University Medical Center, Maywood, IL 60153 and the VA Hospital, Hines, IL. 60141

The present study was undertaken to test the hypothesis that myocardial insulin unresponsiveness develops during sepsis in the conscious dog. Mongrel dogs (N=8) of either sex (20-25kg) were surgically instrumented to measure mean arterial blood pressure (MABP), left ventricular pressure (LVP), LVdP/dt, coronary blood flow and LV wall thickness. A catheter was positioned in the coronary sinus for collecting myocardial venous samples. Arterial glucose concentration was clamped (euglycemic clamp) during a control period and several days following the induction of sepsis. Sepsis was induced by implantation of a human fecal innoculated gauze sponge amid the intestines. Contractility (Ees) was determined over several cardiac cycles by brief aortic occlusion.

	Basal		Peritonitis	
	Control	Clamp	Control	Clamp
Cardiac Glucose uptake (mg/min/100g)	4.4	11.2*	6.0	5.6
Ees (mmHg/mm)	12.8	76*	44*	23*+
MABP (mmHg)	95	110	80*	90+
dP/dt (mmHg/sec)	1077	1480*	962*	1176+

(*=p<0.05 re: basal control; +=p<0.05 re: peritonitis control).

In conclusion, insulin acted as a positive inotrope and increased glucose uptake during the control period. However, insulin resulted in a decrease in contractility without effecting glucose uptake during sepsis. These data are consistent with a myocardial insulin resistance (metabolic and functional).

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40 ADENOSINE POTENTIATES MYOCARDIAL INSULIN RESPONSIVENESS DURING ENDOTOXIN SHOCK. W.R. Law* and R.M. Raymond Depts. of Surgery and Physiology Loyola University Medical Center, Maywood, IL 60153 and the VA Hosp., Hines, IL 60141

Under pentobarbital, adult mongrel dogs (either sex; 19-24 kg) were instrumented to obtain blood samples for measurement of myocardial O_2 (ml/min), glucose (mg/min), and lactate (μmoles/min) uptake. Uptakes were calculated by the product of the appropriate arterial-coronary sinus differences and circumflex blood flow (Q). After basal measurements in control dogs hyperinsulinemic, euglycemic clamp (CLM) was initiated by the i.v. infusion of 4U/min regular insulin and variable amounts of 20% dextrose. Shock (SHK) dogs received an i.v. bolus of S.typhimurium endotoxin (Difco control #743989) after basal measurements. Basal SHK measurements were made 1 hr. post-endotoxin, followed by CLM. In both groups, following CLM measurements, ADO was infused into the circumflex artery for a minimum of 15 minutes (1ml/min; 10^{-2}M) while CLM was maintained. The results are presented below.

	Control (N=6)			Shock (N=3)			
	Basal	CLM	CLM+ADO	Basal	1 hr SHK	CLM	CLM+ADO
Glucose	3.3±.6	6.0±.8	9.9±.8	5.1±.9	2.3±1	4.8±.8	10.6±4.7
Lactate	3.3±.9	3.4±.6	4.4±.6	3.3±.7	3.3±.3	3.8±.2	4.5±.9
Q	54±4	66±5	153±17	62±2.5	35±5.1	62±12	165±18
O_2	6.2±.6	6.0±.3	7.4±.9	7.2±.5	3.6±.4	5.8±1	7.5±3

During SHK, MGU fell below the basal level and insulin was unable to increase MGU above the basal level. However, adenosine infusion during SHK with CLM was still capable of potentiating the response to insulin as it did in control dogs.

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41 PROTECTIVE EFFECTS OF VITAMIN E ON ISCHEMIA-REPERFUSION INJURIES OF THE HEART. W. Mersereau*, R. Abraham*, G. Batist* and R. Chiu. The Montreal General Hospital/McGill University, Montreal, Quebec, Canada.

Ischemia-reperfusion injuries of the myocardium may result in part from membrane lipid peroxidation secondary to the formation of oxygen free radicals. Vitamin E had been shown experimentally to inhibit and terminate membrane lipid peroxidation reactions. We, therefore, studied the protective effects of anti-oxidant, Vitamin E, using an "allo-perfused" rat heart model.

Isolated rat heart perfused by an imbred rat (allo-perfused) was subjected to 20 minutes normothermic ischemia followed by 30 minutes reperfusion. An intraventricular balloon was used to monitor isovolumic cardiac functions, and the results are expressed as "percent recovery" as compared with pre-ischemic values. Gr. I (n=10, control) received no pre-treatment, while Gr. II (n=6) were gavaged with Vitamin E (68 I.U./kg) in sesame oil 24 and 1 hour before the experiments.

RESULTS:	LVP(%)	LVEDP(%)	+dp/dt(%)	-dp/dt(%)	CORONARY FLOW(%)
Gr. I	53.7±9.0	447.5±39.7	53.9±9.1	55.4±9.1	76.2±5.0
Gr. II	91.5±2.7*	127.7±27.1*	91.1±3.7*	97.4±2.6*	90.7±6.4

Data expressed as mean±SEM. *P< 0.05, student's t-test (Gr. I vs Gr. II).

These results indicate that the pre-feeding of Vitamin E can significantly reduce the reperfusion injury following global cardiac ischemia and improve the recovery of cardiac physiologic functions.

42 **BENEFICIAL EFFECTS ON RENAL SYMPATHETIC NERVE RESPONSES TO RA-642 DURING HEMORRHAGIC SHOCK IN ANAESTHETIZED RABBITS.**

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This experiment was designed to evaluate effects of RA-642, a primido-primidine derivative, which is a new central pressor agent, to sympathetic nerve activity during hemorrhagic shock in anesthetized rabbits. Hemorrhagic hypotension to 20-30 mmHg was maintained by means of servo-controlled system. Renal sympathetic nerve activity (RNA) during hemorrhagic hypotension showed a triphasic pattern: initial increase in RNA due to activation of baroreceptor reflex system and second increase, which might be due to brain ischemia, followed by profound decline in RNA. Either RA-642 (0.25 mg/kg i.v.) or vehicle of saline was administered when RNA fell to near noise level and then catheter for the bleeding was clamped. RA-642 caused significant increases in systemic blood pressure (SBP, from 31 to 48 mmHg) and RNA (to 270 % of preinjection level). For comparing with other cardiotonic agents such as dopamine and isoproterenol, we tested effects of these agents on the same experimental condition. However, these cardiotonic drugs did not cause remarkable improvement of SBP and RNA. Thus, these results suggest that RA-642, which causes an augmentation of central sympathetic outflow, may have a tendency for improving cardiovascular deteriorations in late stage of hemorrhagic shock, as a new cardiotonic agent.

43 EFFECT OF BETA-DOSE EPINEPHRINE ON MYOCARDIAL DEPRESSION IN DOGS. R. Rochon*, M. Newbrough*, W. Fallon*, T. Reyna*, (Spon: F. Cerra). William Beaumont Army Medical Center, El Paso, TX 79920-5001.

Myocardial depression is a common event associated with shock of a traumatic or septic etiology. A dog study was designed to study the effectiveness and potential usefulness of beta-dose epinephrine in myocardial depression. By infusing a continous dose of 1-2 mcg/min of epinephrine, beta receptors were selectively stimulated. Anticipated results would be increased cardiac output without untoward alpha side effects (ie., tachycardia, dysrhythmias, or increased afterload). Adult Foxhounds were given general anesthesia and invasively monitored (arterial line and Swan-Ganz catheter). Vascular probes were inserted to assess hepatic, renal, and superior mesenteric arterial blood flow. Acepromazine maleate (.5mg/lb) was administered to induce myocardial depression. The dogs recieving epinephrine demonstrated a reversal in myocardial depression as

opposed to the controls recieveing saline. Cardiac Index rose 1.4 $l/m^2/min$ above baseline depression in the epinephrine cohort. Blood flow in the hepatic, renal, and superior mesenteric arteries was not adversely affected. The heart rate did not change significantly nor were any dysrhythmias noted. A constant infusion of epinephrine at beta-dose range is effective in reversing myocardial depression.

44 VOLUME EXPANSION VERSUS DOBUTAMINE OR NORADRENALINE IN THE TREATMENT OF RIGHT VENTRICULAR (RV) FAILURE IN PORCINE SEPTIC SHOCK

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The purpose of the study was to explore if 1) volume loading in combination with dobutamine (DOBU) or noradrenaline (NORA) would be superior to volume loading alone in the treatment of depressed RV performance in septic shock complicated by acute pulmonary hypertension, 2) NORA would be superior to DOBU because of its direct vasoconstrictor effects on the peripheral circulation and increase in RV perfusion pressure. Experiments were performed on 21 anesthetized ventilated pigs; gated blood pool scans and hemodynamics were performed simultaneously. All animals were given $3-4x10^8$/kg live E.coli which resulted in an abrupt increase in pulmonary arterial pressure whereas mean arterial pressure (MAP), cardiac output (CO) and RV ejection fraction fell. RV end-systolic volume was unchanged, RV end-diastolic volume and RV perfusion pressure decreased. After randomization the control group (n=5) was subjected to volume loading, treatment groups (n=8) received volume loading in combination with DOBU (5-10 ug/kg/min) or NORA (0.25-0.50 ug/kg/min).

In contrast to volume loading DOBU and NORA increased CO and RV ejection fraction but only NORA restored MAP. NORA improved RV performance (RV ejection fraction and RV end-systolic pressure-volume relationship) probably because it increased RV perfusion pressure, especially during diastole. Thus, this suggests that NORA in combination with volume loading is the treatment of choice to restore RV performance under these circumstances.

45 CARDIOVASCULAR EFFECTS OF A NEW SYMPATHOMIMETIC, 2-[(5-CHLORO-2METHOXYPHENYL)-AZO]-1H-IMIDAZOLE (M6434) IN NORMAL AND SHOCKED ANIMALS.

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We have previously reported a vasopressor effect of M6434 through α-adrenoceptor stimulation (H. Ohnishi et al. Artzneim. Forsch. 31, 1425-9, 1981) and a successful salvage of animals from lethal shock by intravenous injection of M6434 at doses ranging from 3 to 10 μg/kg/min (H. Ohnishi et al. Circ. Shock 13, 261-70, 1984). In order to elucidate the mechanism(s) responsible for the beneficial effect on shock models, we investigated the cardiovascular effects of M6434 in normal and shocked animals. In normal dogs, i.v. injection of M6434 at doses ranging from 1 to 30 μg/kg/min increased blood pressure (BP) and total peripheral resistance (TPR) with some decreases in superior mesenteric arterial- and renal cortical tissue-blood flows and cardiac output (CO) at higher doses. In the dogs in severe hemorrhagic shock, M6434 (10 μg/kg /min, i.v.) did not cause significant change in TPR, but increased BP, CO and the survival rate. In hemorrhagic-shocked rats, M6434 (10 μg/kg/min, i.v.) shifted the blood flow distribution from skin and skeletal muscle to several vital organs with increases in BP and CO. The present data indicate that the blood perfusion of vital organs in hemorrhagic-shocked animals can be maintained by the infusion of M6434 though it may be decreased by the excess amount of M6434 in normal animals. This differential effect, which cannot be explained only by α-adrenoceptor stimulation, may contribute to the effectiveness of M6434 on the experimental shock.

46 **THE HEMODYNAMIC EFFECT OF M6434;2-[(5-chloro-2-methoxyphenyl)azo]-1H-imidazole, IN HEMORRHAGIC SHOCK IN DOGS WITH NARROWED CORONARY ARTERY.**

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M6434 has been reported to increase the survival rate in hemorrhagic shock in dogs. The purpose of this study was to determine whether M6434 improved coronary

artery flow in the narrowed coronary artery even in hemorrhagic shock. METHODS Eight mongrel dogs weighing 10-15 kg were used hemodynamic variables included mean arterial pressure (MAP), heart rate (HR), LVEDP, CI, and the left anterior descending coronary (LAD) flow. After control measurement (M1), LAD was constricted to decrease flow to approximately 60% of initial flow. the second measurement (M2) was done after stabilization. MAP was decreased to approximately 50 mmHg by bleeding and kept constant for 10 minutes. Then, the 3rd measurement (M3) was done. The 4th measurement (M4) was done after 5 minutes of intravenous infusion of M6434 (5μg/kg).

RESULTS

	LAD flow (ml/kg/min)	LVEDP (mmHg)	MAP (mmHg)	HR (bpm)	C I (l/min/m^2)	
M1	1.13±0.16	14.3±1.7	102.9±4.2	125±8	2.64±0.22	
M2	0.69±0.13*	17.8±2.4	99.5±5.0	120±7*	2.42±0.18*	
M3	0.24±0.07*	12.1±1.7*	50.6±1.9*	121±7	1.11±0.06*	
M4	0.50±0.09*	18.5±2.2*	102.5±5.2*	115±6	1.44±0.07*	mean ±SEM

*: significant compared with previous value ($p<0.05$) by paired t-test.

CONCLUSION M6434 may maintain coronary blood flow in hemorrhagic shock, which might lead to improve the survival rate.

47 RAT CARDIOVASCULAR ß-ADRENOCEPTOR CHANGES IN FECAL INOCULUM SEPSIS (FIS). K. Blaho*, S. Winbery*, K. McDonough and L. Barker* Depts Pharmacology and Physiology, LSUMC-NO, New Orleans, LA 70112.

Sepsis induced by cecal ligation and puncture produces a supersensitivity in the chrontropic actions of isoproterenol (ISO) on the rat right atrium and changes the response from one mediated by ß1-receptors to one mediated by ß2-receptors (Smith et al.: Am. J. Physiol. 251: H405, 1986; Winbery, et al.,: Circ. Shock 18: 343, 1986). The present studies were undertaken to determine if FIS also produced supersensitivity in right atria and to determine if ISO ß2-mediated vasodepressor responses were altered in septic rats. Forty-eight hr after the induction of FIS, rats were anesthetized with pentobarbital (45 mg/kg, i.p.) and surgically prepared for recording carotid blood pressure and femoral injection of drugs. To minimize relfex activity the animals were treated with hexamethonium (5 mg/kg), dibenamine (3 mg/kg) and yohimbine (1 mg/kg). Diastolic pressure was maintained between 100 - 125 mm Hg by the infusion of angiotensin II (150 nanograms/kg/min). Dose-response curves were generated for the vasodepressor effects of ISO. The ED50 values for ISO induced reduction of diastolic pressure were similar in control and septic rats, 0.14 ±0.02 (N = 4) and 0.19 ± 0.05 nmol/kg (N=3), respectively. Right atria obtained from septic rats 48 hr after FIS were supersensitive to ISO; the EC50 values for FIS and controls were 16 ± 6 pM and 1.4 ± 0.2 nM, respectively. Supersensitivity at right atrial ß-receptors is common to both methods of producing sepsis. Vascular ß-receptor supersensitivity was not apparent in FIS rats. Supported by HL32749.

48 EXERCISE TRAINING AND THE RESISTANCE OF THE HEART OF SHOCK. Peter M.C. DeBlieux*, Steven F. Pflug*, Jimmy N. Ponder*, Raymond E. Shepherd. Dept. of Physiology, Louisiana State University Medical Center, New Orleans, LA. 70112.

The present study determined whether exercise-training protected against endotoxin-induced myocardial dysfunction. After a 12 week treadmill training period, carotid catheters were implanted 24 hr prior to endotoxin administration in sedentary saline (SS), sedentary endotoxin (SE), trained saline (TS), and trained endotoxin (TE) injected animals. Heart rates and mean arterial pressures were monitored 0.5,1,2,3, and 4 hr following endotoxin/saline injection. Plasma catecholamine concentrations were evaluated on blood samples drawn at each time point. Endotoxin caused a mild hypotensive response 1 hr after endotoxin administration; animals were normotensive by 3 hr post-endotoxin. Myocardial performance was studied using the isolated perfused working heart. The product of cardiac output and peak systolic pressure, an index of cardiac work, was 24-32% greater in TS compared to SS. No differences in cardiac performance were evident until 4 hr post-endotoxin when cardiac performance was decreased 32% in TE compared to a 45% decrease in SE. Plasma catecholamines were 5-15 fold higher in SE compared to the other groups at this time point. Cyclic AMP was reduced in myocytes from SE in response to isoproterenol (-28%) and to forskolin (-44%) but was not different in myocytes from TE, TC, and SS after 4 hr endotoxin. These data suggest that the adaptations to exercise attenuate the depressed myocardial performance elicited by endotoxin. This protection may involve a regulatory role of catecholamines on heart function. Differences in cyclic AMP accumulation suggest that training imparts some protection of the beta-adrenergic receptor adenylate cyclase system against endotoxemia. (Supported by GM 35390 and AHA 851256.)

49 MYOCARDIAL BETA ADRENERGIC RECEPTORS (BAR) IN E. COLI INDUCED SEPTIC SHOCK. M.R. Eisinger*, S.B.Jones, M.Westfall* and M.M. Sayeed. Loyola University Medical Center, Maywood, IL 60153.

In rats the administration of i.v. E. coli results in high levels of circulating catecholamines followed by hypoglycemia and shock. We tested the hypothesis that i.v. E. coli and resulting sequelae cause changes in myocardial BAR function and distribution. I.V. E. coli (2×10^{10} organisms/kg) or saline was administered to fed male rats. Hearts were removed when rats were in the agonal stage of septic shock (2.9±0.5 hrs post i.v.) Two left ventricles were used for each preparation of sarcolemmal (SL) and cytosolic (CY) fractions according to the methods of Maisel et al (Science 230:183-186, 1985). Agonist competition curves for each fraction were generated with ^{125}ICYP and increasing concentrations of isoproterenol. Saturation curves were determined with increasing concentrations of ICYP. Results are as follows:

	Total	Sarcolemma	Cytosol
Control (N=3)	305±68*	208±46 (69±4%)	96±28 (31±4%)
Bacteremia (N=4)	233±22	118±8 (51±3%)**	115±12 (49±3%)**

*X±SEM, BAR in fm/mg protein, **$p<0.05$ as compared to control

K_D did not differ significantly in all 4 groups. Agonist competition curves revealed control BAR - SL fraction fit a 2 site curve and could be shifted to a one site curve with the addition of Gpp(NH)p. Two of 4 bacteremic SL fractions revealed a one site curve. All CY fractions showed BAR to best fit a one site curve. The shift in distribution of BAR from the SL to CY fraction and the change in agonist binding suggest that BAR are undergoing desensitization in the agonal stage of acute septic shock. (Supported by NIH Grant HL31163)

50 MYOCARDIAL RESPONSES TO A SUBLETHAL DOSE OF ENDOTOXIN. W. Rumsey* and L. Kilpatrick-Smith Univ. of Pennsylvania School of Medicine, Philadelphia, PA 19104.

The effects of a sublethal dose of endotoxin on the relationship of coronary flow to myocardial O_2 consumption was examined using the Langendorff preparation. Sprague-Dawley rats were injected (IP) with either endotoxin (E, 0.2 mg/kg, Sigma lot#34E4053) or 5% dextrose (C) and fasted overnight. Hearts were paced at 5 Hz and perfused at 72 cm H_2O with Krebs-Henseleit buffer supplemented with 11 mM glucose, 0.2 mM pyruvate and 12 IU/l insulin (G/P) for 40 min and additionally for 20 min with 5 mM acetate (A). As compared to hearts from C animals, those from E rats showed increases in coronary flow (8.3±0.2 (11) vs 11.7±0.2 (13) ml/min/g wet wt, $p<0.001$), O_2 consumption (3.78±0.12 (8) vs 4.42±0.16 (11) umol/min/g wet wt, $p<0.01$) and effluent [O_2] (493±20 (8) vs 577±17 (11) uM, $p<0.001$) with G/P. When A replaced G/P as substrate for hearts from C rats (3), O_2 consumption and flow increased to 4.46±0.11 umol/min/g wet wt ($p<0.05$) and 11.3±1.2 ml/min/g wet wt respectively, and creatine phosphate(CrP)/creatine(Cr) rose from 1.18±0.05 (5) to 1.9±0.03 (3, $p<0.001$) without marked changes in effluent [O_2]. In hearts from E rats (6), the transition to A resulted in enhanced O_2 consumption (5.46±0.22 umol/min/g wet wt, $p<0.001$) and decreased effluent [O_2] (492±21 uM, $p<0.01$), but flow and CrP/Cr remained relatively unaltered. These findings indicate that exposure to sublethal doses of E results in an altered tone of the coronary vessels and that this may inhibit the compensatory vascular response to enhanced cardiac O_2 demands upon A infusion. Our in vitro results may be relevant to the coronary vasodilation observed in patients with sepsis. (Supported by GM 21524 & PO1-NS-17752)

51 ALTERATIONS IN THE INOTROPIC ACTION OF ISOPROTERENOL ON ISOLATED CARDIAC TISSUES FROM SEPTIC RATS. S. Winbery*, K. McDonough and L. Barker*. LSUMC Depts. of Physiology and Pharmacology, New Orleans, La. 70122

We have observed sensitization to the chronotropic actions of isoproterenol (ISO) on isolated right atria from rats made septic either by cecal ligation and puncture (CLP, Circ. Shock 18: 343, 1986) or by fecal innoculum (FI). To assess the effect of sepsis on inotropic actions of ISO, cummulative dose response curves were constructed on papillary muscles isolated from left ventricles of rat hearts 24 hrs after CLP and on isolated left atria from rats 48 hours after FI. The isolated tissues were maintained in Krebs-Henslet solution under 0.5 g of tension and stimulated with square wave pulses (1Hz, 2msec duration, threshold voltage + 20%). The ED50 values for ISO on tissues from septic rats (0.18 ± 0.07 nM, papillary muscle; 0.07 ± 0.01 nM, left atria) was 10 - 20 fold less than the ED50 values for ISO on tissues from sham operated rats (2.4 ± 0.3 nM, papillary muscle; 1.1 ± 0.7 nM , left atria). The maximum increase in isometric tension produced by isoproterenol was 40 to 50 % less for isolated tissues from septic rats (1.3 ± 0.2 g, papillary muscle; 1.2

± 0.2 g, left atria) than for tissues from sham operated rats (2.1 ± 0.2 g, papillary muscle; 2.4 ± 0.3, left atria). In summary, two models of sepsis produced a 10 - 20 fold increase in the potency of ISO simultaneous with a 40 - 50 % decrease in the maximum contractile response of isolated cardiac tissues to ISO. Supported by HL32749.

52 PROSTAGLANDIN INHIBITION IMPAIRS RENAL MICROVASCULAR BLOOD FLOW RESPONSES DURING HYPERDYNAMIC BACTEREMIA. H.M. Cryer*, L.S. Unger*, R.N. Garrison, P.D. Harris. Depts. Surgery and Physiology, Univ. Louisville, Louisville, KY 40292.

The effects of prostaglandin (PG) synthesis inhibition on renal microvascular blood flow responses to sepsis in male Sprague-Dawley rats (N=5) were measured in chronic hydronephrotic kidneys suspended with intact neurovascular connections in an environmentally controlled krebs tissue bath. Diameter and red blood cell velocity were measured in intralobular (IL), afferent (AFF) and efferent (EFF) arterioles by direct in vivo video-microscopy and optical doppler velocimetry during a baseline period, after intravenous infusion of $1x10^8$ live E.coli, and after addition of mefenamate (PG-inhibitor) to the bath (10^{-4} M). Cardiac output (CO) was measured by transpulmonary thermodilution and systemic vascular resistance (SVR) was calculated. Results expressed as percent (%) of baseline values were:

	CO(ml/min)	SVR(RU)	FLOW	IL(μ)	AFF(μ)	EFF(μ)	MAP(mmHg)
Baseline	110±5	.78±.04	100%	29±5	9±2	12±1	85±4
E.coli (40 min)	*127±4%	*75±2%	*57±11%	*84±3%	*88±2%	103±2%	100±4%
Mefenamate (10 min)	115±6%	97±6%	*†33±12%	*69±8%	*77±6%	100±4%	*112±4%
Mefenamate (30 min)	*114±5%	*93±2%	*†19±6%	*†56±8%	*†67±7%	100±2%	108±4%

* = p<.05 from baseline values, † = p<.05 E.coli compared to mefenamate

These data indicate that E.coli infusion increased CO and decreased SVR, while renal microvascular flow decreased due to preglomerular arteriolar constriction. Mefenamate decreased blood flow further as arteriolar constriction increased to suggest that PG production is an important mechanism for supporting renal microvascular blood flow during high cardiac output sepsis (VAMC; AI22098).

53 **EFFECT OF ENDOTOXIN (LPS) TOLERANCE (TOL) ON ARACHIDONIC ACID (AA) TURNOVER IN MACROPHAGE (MΦ) PHOSPHOLIPID POOLS.** T.S. Rogers*, J.A. Cook, W.C. Wise and P.V. Halushka. Medical University of South Carolina, Charleston, S.C. 29425

Peritoneal MΦ from LPS Tol rats exhibit decreased AA metabolism to prostaglandins and thromboxane in response to diverse stimuli that cannot be attributed to depletion of endogenous AA. The effect of Tol on ^{14}C-AA incorporation into and release from phospholipid pools (15 min to 24 hrs) was determined. Tol did not affect the total amount of ^{14}C-AA incorporated but did alter temporal incorporation into individual phospholipids. ^{14}C-AA incorporation was increased in phosphatidylcholine (PC) and phosphatidylethanolamine (PE), reduced in phosphatidylserine (PS) ($p<0.05$), and exhibited little change in phosphatidylinositol (PI). The release of ^{14}C-AA after 24 hr incorporation from phospholipids was determined in response to LPS (50 μg/ml) and calcium ionophore A23187 (1 μM).

% DEPLETION OF ^{14}C-AA FROM PHOSPHOLIPID POOLS [a]

		PC	PS	PI	PE
LPS	**CON**	**35.5 ± 5.7 %**	**N.D.**	**6.3 ± 1.7**	**10.3 ± 3.3**
	TOL	**9.9 ± 3.8 ***	**N.D.**	**N.D.**	**N.D.**
A23187	**CON**	**23.0 ± 6.0**	**12.2 ± 3.2**	**10.1 ± 3.1**	**29.3 ± 3.0**
	TOL	**26.0 ± 3.4**	**N.D.**	**N.D.**	**22.3 ± 4.4**

a. % = CPM in unstimulated MΦ/ CPM in stimulated MΦ x 100; data are epressed as mean ± S.E.M., N = 6 - 8 / group. * p< 0.05. N.D. = nondetectable.

These data demonstrate that LPS Tol alters AA uptake and release from phospholipids of MΦ. The results suggest that changes in phospholipid turnover and/or compartmentalization are associated with the Tol state. (Supported by NIH GM27673 and HL29566).

54 PROLONGED IMPAIRMENT OF NATURAL KILLER (NK) CELL ACTIVITY FOLLOWING SIMPLE HEMORRHAGE. R. N. Stephan*, W. J. Poo*, C. A. Janeway*, S. S. Zoghbi*, R. E. Dean*, A. S. Geha*, and I. H. Chaudry. Michigan State Univ., East Lansing, MI, 48824, Yale Univ., New Haven, CT, 06510, and Case Western Reserve Univ., Cleveland, OH, 44106.

Maintainance of an intact NK effector system prevents both infection and tumor occurance. It is unknown, however, whether simple hemorrhage without major tissue trauma produces any impairment of the cytolytic ability of the NK cells. To study this, endotoxin resistant C3H/HEJ mice were bled to and maintained at a mean BP of

35mmHg for 1 hr following which they were adequately resuscitated. Control mice were not bled but otherwise treated identically. Immediately after hemorrhage (without resuscitation) (time zero) and on days 1, 2, 3, 5 and 6 following hemorrhage and resuscitation, splenic cells were isolated and cytotoxicity measured using ^{51}Cr release assay. YAC-1 tumor cell line served as target. Target: effector ratios were established at the level of 30% killing of the YAC-1 cells. The results (mean ± S.E.) were evaluated by using the one way analysis of variance.

	TARGET:EFFECTOR RATIO X 10^{-3} AT 30% KILLING LEVEL		
CONDITIONS	TIME ZERO	DAY 1 AFTER RESUSCITATION	
Controls	94.35 ± 6.05	94.35 ± 6.05	*p < 0.01 compared
Hemorrhage	64.18 ± 5.38*	29.69 ± 1.45*	to control.

None of the hemorrhage groups attained a 30% killing level at any target: effector ratio on days 2, 3, 5 and even 6 after hemorrhage and resuscitation. Thus, the NK effector system undergoes a profound and prolonged depression following simple hemorrhage despite adequate resuscitation.

55 HYPOPERFUSION OF THE INTESTINAL MICROCIRCULATION DURING HIGH CARDIAC OUTPUT LIVE E. COLI SEPSIS IN RATS. PW Whitworth*, RN Garrison, HM Cryer*, TE Baumgarten* and PD Harris. Depts. of Surgery and Physiology, Univ. of Louisville, Louisville, KY 40292.

Controversy exists concerning the status of intestinal blood flow during bacterial sepsis. In order to determine if intestinal vasoconstriction and hypoperfusion occur during normotensive, high cardiac output (CO) sepsis, we measured microvascular diameters and blood flows at different levels of the intestinal microcirculation during live E. coli sepsis. Male Sprague Dawley rats (N=10) underwent precollicular brainstem transection to allow study free of drug anesthesia. A loop of small intestine was suspended (with intact neurovascular connections) over an optical port in a temperature, PO_2, PCO_2, and pH controlled Krebs-buffer bath. The microcirculation was observed by optical doppler velocimetry and by video microscopy at a magnification of 1500X. Baseline measurements were made of red cell velocity and microvessel diameters in a major inflow arteriole and its subsequent branches until the vessel entered a villus. CO was measured by transpulmonary thermodilution. After baseline measurements, rats received $6x10^8$ live E. coli by intravenous injection. Measurements were repeated at 15-minute intervals for two hours. Results showed that CO increased by 20% and systemic vascular resistance decreased by 20%. However, microvascular blood flow to the small intestine decreased by 27% at one hour and by 56% at two hours. Marked progressive arteriolar constriction (25-50%, $p < .05$) occurred at all levels of the microcirculation. These data document for the first time that intestinal hypoperfusion caused by arteriolar constriction occurs during high CO sepsis. This hypoperfusion could account for the mucosal injury and barrier dysfunction noted during hyperdynamic sepsis.

56 POSTISCHEMIC TREATMENT IN ANIMAL MODELS OF REPERFUSION INJURY. Stephen F. Badylak. Purdue University, West Lafayette, IN 47906

Four studies utilizing three different models of reperfusion injury were done to determine the effectiveness of allopurinol and oxypurinol (xanthine oxidase inhibitors, 25 mg/kg), deferoxamine, (an iron chelator, 50 mg/kg), and DMSO (a putative free radical scavenger, 50% solution, 1 ml/kg) for protecting against reperfusion injury when administered after the ischemic period. The four studies included a rat model of cardiorespiratory arrest and resuscitation (7 min. arrest. 10 day survival), two rat isolated heart preparation studies (60 min. ischemia, 60 minute reperfusion), and a study of complete renal ischemia in the rat (45 min. ischemia, then reperfusion and 10 day survival). Results of all studies consistently showed protection by allopurinol, oxypurinol, and deferoxamine, but not DMSO ($n = 10$ in all studies). Ten day survival was significantly increased ($P < 0.01$). myocardial CPK release was decreased ($P < 0.01$), myocardial function was preserved ($P < 0.01$), plasma creatinine levels were less ($P < 0.01$), and quantitative morphologic studies showed preserved architecture in the treated groups of the respective studies. We conclude that protection against reperfusion injury is possible in a clinically realistic time frame, that is after the ischemic injury, and that pretreatment is not required. Furthermore, it is suggested that protection is afforded by inhibiting specific steps of a xanthine oxidase-mediated, iron-catalyzed free radical mechanism of injury.

57 ETHANE IN EXPIRED AIR DURING SHOCK IN RATS. I. Cangiano, P. Angiolini, G. Consales and G.P. Novelli. Institute of Anesthesiology and Intensive Care - University of Florence - 50134 Florence (Italy).

The hypothesis of an umbalance between generation and scavenging of oxygen free radicals during shock is supported by a lot of experimental data. One of the mechanisms of damage induced by oxygen free radicals is lipid peroxidation of cell membranes. Ethane exhalation has been used as an "in vivo" marker of this phenomenon in rats submitted to traumatic or endotoxic shock.

METHODS. Experiments were performed on Wistar male rats (200 g. weight). Traumatic shock was provoked by a rotating drum. Endotoxic shock was provoked by E. Coli lipopolisaccaride (Difco 055 B4 20 mg/Kg i.p.).

Ethane exhalation was evaluated using the method described by Lawrence and Cohen, partially modified. Traumatized, endotoxiemic or control rats were allowed to breathe in a collecting chamber hermetic sealed, and ethane was concentrated in a vial of activated charcoal inserted in the breathing circuit. Vials were changed every hour and ethane was analyzed by gas chromatography.

RESULTS. Ethane exhalation was largely increased in both types of shock in respect to control rats and it was related to worsening of shock.

CONCLUSION. The progressive increase of lipid peroxidation is indicative of an oxygen radicals umbalance during traumatic and endotoxic shock in rats.

58 **ASPECTS OF THE MITOCHONDRIAL OXIDATIVE DAMAGE IN HUMAN CIRCULATORY SHOCK.** G.G. Corbucci*, A. Gasparetto*, M. Antonelli*, M. Bufi* and R.A. De Blasi (SPON: A.M. Lefer). Institute of Anaesthesia and Resuscitation, University "La Sapienza", 00161, Rome, Italy.

In the present study, we examined the metabolic connections between the electron carrier activities and the Krebs cycle efficiency during the course of circulatory shock in human skeletal muscle biopsies. In 10 shock patients, muscle needle biopsies and plasma samples were collected at three hour time intervals following the onset of shock for a duration of 24 hours. A significant fall in cytochrome c oxidase and succinate dehydrogenase activities occurred in agreement with the decrease in the activities of the total and oxidized Coenzyme Q_{10}. Although these findings are significant, the crucial point seems to be inactivation of succinate-dehydrogenase (SDH). This finding is also consistent with the high levels of succinate and the markedly reduced levels of fumarate. The content of other tricarboxylic acids reflects the dehyrogenase inactivation, and this event could be related to the iron content in terms of the close relationship between the dehydrogenase activities and iron metabolism. The results obtained, compared with the data on the oxy-radical activities, seems to focus attention on the metabolic changes due to shock and lead to a consideration of oxy-radical damage as a consequence of the impairment of mitochondrial oxidative capacity. Thus, skeletal muscle mitochondrial dysfunction appears to be an important consequence of circulatory shock in humans which may help elucidate the biochemical abnormalities of severe shock in humans.

59 OXYGEN FREE RADICALS IN A LD-50 MODEL OF INTESTINAL SHOCK. Eva Haglind, Ulf Haglund, Dept. of Surgery I, Sahlgrenska sjukhuset, S-413 45 Göteborg, Sweden.

Oxygen radicals have been implicated in the pathophysiology of intestinal mucosal lesions after intestinal ischemia. In a model of graded intestinal vascular obstruction we found mucosal lesions, cardioinhibitory substances and mortality. Groups with high pressure on the mesenteric vessels and high mortality had severe mucosal lesions before reperfusion. Studying different pressures and durations we found protective effects of scavengers. Most effects were found in a LD-50 model. The aim of this study was to determine effects of allopurinol(allo), superoxidedismutase SOD or SOD +catalase(cat) in the LD-50 model concerning circulation and mucosal lesions.

Shock was induced in Wistar rats by 100 cm H_2O on the mesenteric vessels for 60 min. 4 groups were studied: Shock(n=8) no infusion; S-allo (n=8) 5 mg allo/g bw 20 min before experiment started; S-SOD(n=8) 0,5 mg SOD/100 g bw 10 min before reperfusion+infusion 0,5 mg/100 g bw/10 min; S-SOD+cat (n=10) SOD as above+2 mg cat 100 g bw exactly as SOD. Blood pressure(BP), hematocrit (Hct), fluid leaking from intestinal serosal surface and degree of small intestinal mucosal injury were determined. The animals were killed 25 min after reperfusion.

Hct increased (by 7%-14%) in all groups. Fluid leakage was larger in S-SOD+cat 0.128 ±0.036g/100 g bw) than in Shock(0.049±0.007). BP increased in S-SOD and S-SOD+cat 74±4:82±5) (at 85 min) but remained unchanged in Shock and S-allo (68±3:62±6). Intestinal mucosal lesions were less severe in S-SOD and S-SOD+cat groups. Results support concept that oxygen free radicals are of importance for the development of mucosal lesion and shock in this experimental model.

60 THE SPIN-TRAPPER PHENYL-BUTYL-NITRONE(PBN)PREVENTS AND REVERTS TRAUMATIC SHOCK
G.P.Novelli,R.Tani,L.Bordi,P.Livi,P.Angiolini and G.Consales. Institute of Anesthesiology and Intensive Care - University of Florence - I-50134 Florence (Italy)
To test the role of oxygen radicals in experimental shock the spin-trapper PBN was used as a scavenger in the aim to"capture"or to"trap"radicals immediately after their generation.
Method:rats were submitted to whole body trauma (rotating drum)during light anesthesia (pentobarbital)so to provoke a 100% lethal traumatic shock.The spin-trapper PBN was given i.p.10 minutes before or 30-60 minutes after trauma.Survival until the 24th hour was measured in PBN treated rats and in control ones receiving the solvent alone.Hematocrit,pH and base-excess were measured in arterial blood of rats different from those used to measure survival.Fluids or drugs were never given.
Results:no adverse effect of PBN was observed.All PBN treated rats (both before and after trauma)survived;all control rats died.Metabolic acidosis and hemoconcentration were prevented or corrected toward normal values by administration of PBN.
Conclusion:the pharmacology of PBN has been never studied however the trapping action on oxygen radicals is accepted.Therefore here reported results confirm the role of oxygen radicals in the pathogenesis of experimental traumatic shock in rats.

61 IMPROVED HEPATIC RECOVERY FROM HYPOTHERMIC ISCHEMIA WITH ATP PLUS ALLOPURINOL
Y. Ohtake, T. Yonko* and M. Clemens. Johns Hopkins Sch Med, Baltimore MD 21205
Although post-treatment with ATP-$MgCl_2$ following organ ischemia has been shown to exert beneficial effects, pre or concurrent treatment has yielded less consistent results. To test whether this might be the result of metabolites of ATP providing substrate for O_2 free radical production via xanthine oxidase, the effect of allopurinol (AL) on ATP effects was studied. Livers were isolated from male Sprague-Dawley rats, flushed with Ringer's and then infused with either Collins Solution (C) (Mg=15mM), C + ATP (3mM), C + AL (0.5 mg/ml) or C + ATP + AL. The livers were then stored at 4° for 26 hours followed by perfusion at 32° C for 120 min in a non-recirculating system with Krebs-HCO_3 with 5 mM lactate and 50 uM taurocholic acid added. Results: (* = $p < .05$ compared to C)

	Bile (ul/15 min)	Wet/Dry wt.	Glucose (umole/g/hr)
C (n=9)	87 ± 18	4.59 ± .31	14.2 ± 3.1
C + AL (n=9)	80 ± 22	4.15 ± .13	9.8 ± 2.3
C + ATP (n=10)	68 ± 17	4.35 ± .14	16.5 ± 3.6
C + ATP + AL (n=7)	145 ± 10*	3.91 ± .07*	20.1 ± 3.3
Control (n=10)	156 ± 15*	3.86 ± .08*	25.1 ± 3.1*

These results indicate that neither AL nor ATP alone produced a consistent improvement in functional recovery. The combination, however, resulted in function similar to livers perfused without prior ischemia (Control). Whether this synergistic effect of AL is the result of decreased free radical generation or salvage of purine remains to be determined. (Supported by NIH Grant #DK 38201)

62 COMPLEMENT ACTIVATION AND LIPID PEROXIDATION IN A RAT MODEL OF MULTIPLE ORGAN FAILURE.
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Multiple organ failure (MOF) is generally attributed to bacterial infection, although there is evidence that non-septic events - generalized inflammation reactions - could contribute to the picture of MOF. Therefore a model in rats (36 animals) was set up, which simulates clinical MOF by intraperitoneal application of zymosan (mortality - 14 days = 36 %).
To obtain further insight into the mechanisms involved, special emphasis was put on complement activation (CH50), granulocyte activation (superoxide release)

and lipid peroxidation (thiobarbituric acid reactive material TBA-R). Results:

Day	CH50	PMN/ul	Superoxide n.stimul.	nmol/10^6PMN PMA stimul	nmol/ g liver	TBA-R nmol/ g lung	TBA-R nmol/ ml plasma
contr.	97	3251±600	10± 3	102±37	5.4±0.3	14.8± 4	3.4±0.6
2	70±6	461±116	51±19	232±59	229.2±51	226.9±66	7.8±1.5
4	76±5	5772±951	3± 1	19± 5	64.7±30	104.3±39	47.1±15

There is a coincidence of lowest CH50 with smallest number of circulating PMN, but their highest activation stage (superoxide) on day 2. At the same time, peak concentrations of TBA-R in tissue and somewhat delayed peak levels of TBA-R and N-Acetylglucosaminidase (NAG) in plasma are noted (day 9 and 14 not shown). Since recent overall results e.g. mortality are similar to the previous ones in either normal or germ-free rats (Goris et al. Arch. Surg. 1986) we conclude that generalized inflammatory reactions without septic events might be responsible for MOF.

63 EFFECTS OF SEPTIC SERA ON INTRACELLULAR CALCIUM, pH, AND PEROXIDE OF ISOLATED AND CULTURED RAT HEPATOCYTES. T. SATO, T. NISHIHIRA*, K. KOIZUMI* and B.F. Trump. Department of Pathology, University of Maryland and MIEMSS, Baltimore, MD 21201.

Hepatocellular dysfunction and injury are frequently seen during sepsis. In addition to the altered hemodynamics and bacterial components, various humoral factors are implicated as a primary or secondary cause of cell injury during severe infection and sepsis. In the present study, therefore, the direct effects of septic sera, freshly obtained from acute lethal bacteremic rats, on various parameters of hepatocytes were studied using fluorospectrophotometry. Rat hepatocytes, either freshly isolated or cultured overnight, were used. Septic sera were obtained from rats subjected to lethal E. coli bacteremia. Saline injected rats were used as controls. Septic serum was steriled through membrane filtration (0.22 um). For measurement of intracellular ionized calcium $[Ca^{2+}]_i$, cells were loaded with 25 um Quin 2 AM for 45 min. As an intracellular pH indicator, cells were loaded with 5 uM of fluorescent probe BCECF for one hr. After loading with either Quin 2 or BCECF, the cells were washed and treated with septic sera. As a peroxide indicator, the fluorescent probe 5(and 6)-carboxy-2',7' dichlorofluorescin was added at a concentration of 2 uM to the incubation medium. Following treatments, changes in the intensity of fluorescence were continuously recorded. Results indicated that septic sera 1) induced an early increase in $[Ca^{2+}]_i$, 2) increased the intracellular pH, and 3) enhanced the production of hydrogen peroxide. Thus, septic sera can directly affect hepatocytes, possibly altering the plasma membrane integrity through peroxidation by noxious factor(s). (Supported by NIH GM 32084).

64 OXYGEN CONSUMPTION AND CO2 PRODUCTION IN CANINE HEMORRHAGIC SHOCK. E. BENJAMIN, T.J. IBERTI, K.M. KELLY*, D.P. KATZ*, M.J. ROSEN*. DEPARTMENTS OF SURGERY & ANESTHESIOLOGY, THE MOUNT SINAI MEDICAL CENTER, NEW YORK, N.Y. 10029.

In a canine hemorrhagic shock model, we studied the time course of systemic oxygen consumption ($\dot{V}O2$) and CO2 production ($\dot{V}CO2$) to determine the relative contribution of aerobic and anaerobic metabolism. Six dogs were anesthetized, paralyzed, ventilated and hemodynamically monitored. Respiratory gases were analyzed using a Metabolic Gas Monitor II (Utah Med), Hypotension was induced and maintained at 40-45 mmHg by controlled hemorrhage, and values followed for 6 hr. Shock was associated with significant metabolic acidosis secondary to hyperlactatemia. ($*p < 0.05$).

VARIABLES	BASELINE	HGE + 1H	HGE + 3H	HGE + 5H
BLOOD LOSS	67 ± 103	892 ± 162	833 ± 374 *	983 ± 150 *
CI	4.3 ± 0.9	0.9 ± 0.3 *	1.2 ± 0.2 *	1.2 ± 0.3 *
PvO_2	68 ± 11	27 ± 5 *	29 ± 4 *	28 ± 5 *
$PvCO_2$	42 ± 4	69 ± 10 *	72 ± 10 *	64 ± 11 *
VO_2	94 ± 25	75 ± 25	83 ± 25	84 ± 24
VCO_2	82 ± 18	64 ± 18	85 ± 25	88 ± 25
RQ	.87 ± .06	.85 ± .07	1.03 ± .15 *	1.04 ± .08 *

The results demonstrate that a significant increase in CI had little effect upon $\dot{V}O2$, and that preservation of aerobic metabolism was the result of increased O2 extraction. The increased $\dot{V}CO2$ may be one of the causes of venous hypercarbia. It is unclear whether the increased RQ is due to aerobic combustion of predominantly CHO fules, from anaerobic decarboxylation, or from lactic acid buffering.

65 VASODILATOR CHARACTERISTICS OF HYPERTONIC SODIUM ACETATE AND SODIUM CHLORIDE: EFFECTS OF AUTONOMIC BLOCKADE. -A.M.Bessa;M.A.Saragoça;M.L.Cezaretti;J.B.Almeida;M.P.S.G.Amorim;S.A.Draibe and O.L.Ramos; (Spon:M.R.Silva).- Nephrology Division, Escola Paulista de Medicina. São Paulo, SP, Brazil.

Hypertonic sodium acetate (SA) and sodium chloride (SC) increase cardiac output and induce vasodilation but SA has a greater vasodilatory action than SC and promotes hyperkinectic circulation. This difference is attributed to vasoconstriction secondary to sympathetic stimulation by SC administration.We thus compared graded hyperosmolar infusions (1125 to 9000 mOsm/L), of SA (group A,n=8) and SC (group B,n=7) in dogs. SA was administered without or with beta (group C,n=6) and alpha (group D,n=6)blockade with. We measured cardiac output(CO), arterial pressure(AP) and calculated total peripheral resistance (TPR) mean transit time (MTT) and a ratio of stroke volume to cardiopulmonary volume (SV/CPV). Group A had greater changes than Group B in CO(Δ= 2.06±0.36 vs +0.46±0.30L/min,$p<0.001$), in TPR(Δ= -28.4±7.5 vs +4.3± 7.8 AU, $p<0.001$),and in MTT(Δ= -3.9±0.46 vs -1.59±1.12 sec, $p<0.001$). Groups C and D had significant changes in CO(Δ= +1.32±0.49 and +1.37±0.13 respectively, $p<0.001$ for both),TPR(Δ= -56.8±18.1 and -39.0±.2 AU respectively, $p<0.001$ for both) and MTT (Δ= -4.33±1.11 and -2.7±0.32 sec respectively, $p<0.001$ for both). Neither of these changes were significantly different from those observed in group A. Increases in SV/CPV were significantly greater in group A than in group B(Δ= +9.0±0.6vs+2.1±1.2,p 0.001), but were similar to those observed in groups C and D (Δ= +6.33±1.9 and +10.0± 2.8 respectively). These results show that the differences in hemodynamic actions of hypertonic SA and SC are not due to interference of the sympathetic nervous system but are possibly related the ability of SA to induce hyperkynetic circulation.

66 **IS THE OUTCOME FROM SHOCK RELATED TO EXTRAVASCULAR LUNG WATER?** U.B. Brückner*, M. Albrecht*. Dept. Exp. Surg., Univ. Heidelberg, 6900 Heidelberg/FRG.

The measurement of extravascular lung water (EVLW) in patients is not a routine procedure though pulmonary edema is supposed to be relevant for the final outcome from shock. A study in dogs submitted to traumatic-hemorrhagic shock (MAP 40 mmHg, uptake 20%) was performed to answer the question: Is outcome during an observation period of 72 hrs related to pulmonary edema?

In 11 anesthetized foxhounds the cisterna chyli was cannulated (standardized surgical trauma) followed by hemorrhagic shock. After primary resuscitation with autologous blood and albumin solution (5%) both, cardiac output and central venous pressure were maintained by additional albumin. EVLW was measured in vivo (dye/thermo) as well as post mortem (gravimetry). Data were collected prior to and during shock, and hourly after resuscitation during the 72-hrs period. In addition, regional organ blood flow (RBF) was determined by means of radio-labeled microspheres (15 µm).

Four dogs survived 72 hrs (S) while 7 animals died within 44 hrs (N). EVLW remained increased ($p < 0.01$; compared with basal values) in both groups during the first 24 hrs (S: 13.6 + 3.9 vs. N: 14.0 + 3.4 ml/kg), but declined to pre-shock values (S: 7.0 + 1.8 vs. N: 7.8 + 2.3 ml/kg) irrespective of non-survival. Non-surviving differed from surviving animals at 24 hrs by lower cardiac output ($p < 0.05$) and increased pulmonary vascular resistance. RBF in bowel and kidney was lower ($p < 0.01$) in the non-survivors already at 12 hrs.

From this study **we conclude:** Final outcome from traumatic-hemorrhagic shock does not depend upon changes of extravascular lung water during and after shock.

67 EFFECTS OF HESPAN ON SERUM AND LYMPHATIC ALBUMIN, GLOBULIN AND COAGULANT PROTEIN. R. Denis*, C. Lucas, A. Ledgerwood, D. Grabow*. Wayne State Univ. Detroit, MI 48201

The effects of Hespan resuscitation on serum and lymphatic proteins following hemorrhagic shock (MAP = 60 torr/90 min, then, 40 torr/30 min) was studied in 34 splenectomized dogs (18-26 kg). Following shock, 5 randomly assigned treatment groups received the shed blood plus 50 ml/kg of the test solution (salt solution (BES) or salt solution with varying concentrations (0.22 gm/kg - 1.5 gm/kg) of Hespan (BES/H). Each dog received 50 ml/kg/day of the test solution for 3 days. Total protein (TP), albumin (A), globulin (G), coagulation protein activity of fibrinogen (F), prothrombin (II), Factor VIII (VIII) and antithrombin III (ATIII) were measured on serum pre-shock, post-resuscitation (PR) and on day 3 and on thoracic duct lymph on day 3. BES/H lowered serum proteins PR when compared to BES alone (Table), and they remained decreased on day 3; the lymph TP and A rose in all BES/H groups whereas coagulation protein activity was insignificantly increased on day 3. This decrease in serum proteins and increase in lymph proteins parallels results with albumin resuscitation and suggests BES/H induces an oncotic extravascular protein relocation.

Groups	TP(gm%)	A(gm%)	G(gm%)	F(Sec)	II(Sec)	VIII(Sec)	ATIII(Sec)
BES	6.5	2.8	3.7	11.3	18.7	28.8	104
BES/H (0.22 gm/kg)	3.3*	1.7**	1.6**	12.9	19.1	39.0*	100
BES/H (0.45 gm/kg)	4.1**	1.9**	2.3**	13.8	20.1	31.4**	72**
BES/H (0.9 gm/kg)	3.8**	1.6**	2.3**	18.8**	19.3	36.8**	89
BES/H (1.5 gm/kg)	3.3**	1.5**	1.7**	18.4**	21.5**	38.3**	81*

* = < 0.05, ** = < 0.005 when post-resuscitation BES/H compared to BES.

68 COMPARATIVE EFFECTS ON RENAL FUNCTION OF WHOLE BLOOD RETRANSFUSION AND LOW MOLECULAR WEIGHT DEXTRAN(ISODEX)IN THE TREATMENT OF SEVERE HEMORRHAGIC SHOCK. - S. A. Draibe; M.A.Saragoça;J.B.Almeida;M.P.S.G.Amorim;M.L.Cezaretti;A.M.A.Bessa;O.L.Ramos; (Spon: M.R.Silva).-Nephrology Division, Escola Paulista de Medicina. São Paulo, SP, Brazil.

The adverse rheological properties of blood during treatment of hemorrhagic shock with whole blood retransfusion may cause impairment of renal function.We thus compared the cnanges induced in glomerular filtration rate (GFR), sodium excretion (UVNa) and sodium excretion fraction(EFNa)in dogs after total retransfusion of whole blood (WB,n=10) and equal volumes of Dextran (MW=40.000), (D40,n=10). After a period of anuria, urine output (V') was partially restored by treatment in WB ($\Delta V'$= -0.23±0.09 ml/min,$p<0.001$) and in D40 ($\Delta V'$= -0.16±0.09 ml/min,$p<0.001$).These changes were similar in both groups. However, GFR did not change signifiantly with D40 (%ΔGFR= -22.8 ±20.7%,n.s)but was significantly reduced with WB(%ΔGFR= -51.7±14.5%,$p<0.001$),but EFNa was not significantly affected in D40 (from 1.15±0.23 to 1.25±0.65%, ns) or with WB (from 1.04±0.27 to 1.70±0.74%,ns. The final hematocrit with D40 was significantly lower than with WB (16.8±1.2 vs 39.3±2.1% respectivelly,$p<0.001$). These results show that renal function is impaired markedly, although in a transient form during treatment of hemorrhagic shock with whole blood retransfusion and that this is not observed with treatment with low-molecular weight Dextran. This difference may be due to better renal flow conditions with D40.

69 EFFECTS OF SODIUM BICARBONATE IN CANINE HEMORRHAGIC SHOCK. T.J. Iberti, E.Benjamin, D.R. Gentili*, K.M. Kelly*, M.J. Rosen*. Departments of Surgery & Anesthesiology, The Mount Sinai Medical Center, New York, NY 10029.

We studied the use of sodium bicarbonate (NaHCO3) administration in a canine model of hemorrhagic shock to determine its effect on lactic acidosis, serum bicarbonate, pH, and cardiac output. Thirteen dogs were anesthetized, paralyzed, mechanically ventilated and hemodynamically monitored. Hypotension was induced and maintained at a MAP of 40-45 mmHg by controlled hemorrhage and reinfusion. After 2.5 hr of shock, the dogs were randomized in 2 groups: A=6 control dogs received NaCl infusion; B=7 dogs received NaHCO3 1mEq/kg followed by a continuous infusion of 2.5 mEq/kg/hr for 2.5 hr.

VARIABLES (MEAN ± SD)		BASELINE	HEMORRHAGE ONLY	HEMORRHAGE + TREATMENT
CI	A	4.3 ± 0.9	1.1 ± 0.1	1.2 ± 0.3
CI	B	4.2 ± 1.3	1.0 ± 0.2	1.3 ± 0.3
LACT	A	0.9 ± 0.4	6.8 ± 0.9	5.1 ± 1.2
LACT	B	0.7 ± 0.4	7.1 ± 3.1	10.1 ± 3.2 *
HCO_3^-	A	20.1 ± 1.8	13.4 ± 1.6	13.6 ± 2.0
HCO_3^-	B	20.1 ± 1.8	11.1 ± 3.0	13.3 ± 2.3
pH	A	7.34 ± .03	7.09 ± .07	7.17 ± .04
pH	B	7.37 ± .02	7.03 ± .10	7.16 ± .10

Results:
*=$p<0.05$

As in other models of lactic acidosis (hypoxic and phenformin induced), this model demonstrates an increase in lactic acid associated with NaHCO3 administration. Although the pathophysiologic mechanism is unclear, it may be related to a decreased intracellular pH due to diffusion of CO2.

70 A POSSIBLE MECHANISM OF HEPATIC FAILURE AFTER HEMORRHAGE IN THE CIRRHOTIC LIVER I.Ikai*, Y.Shimahara*, S.Wakashiro*, N.Ozaki*, Y.Tokunaga*, A.Tanaka*, Y.Kamiyama, K.Ozawa*, Department of Surgery, Kyoto University, Kyoto, 606, Japan

Hepatic energy metabolism based on the mitochondrial functions were investigated to clarify the mechanism of hepatic failure after hemorrhage in cirrhotic liver. Hemorrhagic shock was produced according to Wiggers' model (mean arterial blood pressure:30mmHg) in normal and CCl_4-induced cirrhotic rats. After 120 minutes, the shed blood was returned. Energy charge (EC;ATP+0.5ADP/ATP+ADP+AMP), ketone body ratio (KBR;acetoacetate/3-hydroxybutyrate) which reflects mitochondrial redox sta

(NAD^+/NADH), and phosphorylation rate of isolated mitochondria (PR) were measured in the liver. Values in normal rats are in parentheses. Mortality rate during the shock was 20% in the cirrhotic rats,while 0% in the normal rats.

		E C	K B R	PR nmol/mg/min
preshock		0.81 (0.86)	0.65 (0.73)	116.0 (110.7)
shock	60min	0.46 (0.62)	0.17 (0.29)	63.3 (103.2)
	120min	0.34 (0.34)	0.09 (0.09)	75.5 (65.5)
after reinfusion	5min	0.78 (0.86)	0.33 (0.81)	83.4 (112.2)
	30min	0.82 (0.86)	0.43 (0.77)	86.4 (118.7)

In cirrhotic rats, EC, KBR, and PR during the shock decreased more rapidly than those in normal rats and recovered very slowly after the reinfusion of shed blood. In conclusion, energy metabolism in the cirrhotic liver is severely deteriorated by hemorrhagic shock, concomitant with an impairment of hepatic mitochondria. Such phenomena might be related to a high mortality in hemorrhage in the liver cirrhosis.

71 THE EFFECT OF HYPERTONIC SALINE AND MAST ON UNCONTROLLED HEMORRHAGIC SHOCK IN THE RAT. MM Krausz, EH Landau*, A. Assalia*, D. Gross*, Hadassah University Hospital, Jerusalem, Israel, 91120.

The increase of mean arterial pressure (MAP) and vasodilation induced by hypertonic saline infusion in hemorrhagic shock may augument blood loss from injured vessels. This may be caunteracted by MAST. Rats were devided into 9 groups: gr.1 (n=10)- Controlled hemorrhage (CH) induced by bleeding of 20 ml/kg through an arterial cannula, gr.2 (n=7)- CH treated by 5 ml/kg NaCl 0.9% (NS), gr.3 (n=8)- CH treated by 5ml/kg NaCl 7.5% (HS), gr.4 (n=9) uncontrolled hemorrhage (UH) induced by incision of the ileocolic artery, gr.5 (n=9) - UH treated by NS, gr.6 (n=18) - UH treated by HS, gr.7 (n=6) - UH treated by MAST inflated to 50 torr, gr.8 (n=6) - UH treated by MAST and NS, gr.9 (n=6)- UH treated by MAST and HS. CH led to a fall in MAP to 35 torr followed by a gradual rise to 60 torr ($p<.005$) after 3 h. Infusion of HS led to a rise to 81 torr ($p<.001$) without mortality. During UH a similar fall in MAP to 39.3 torr was followed by spontaneous rise to 66.8 torr ($p<.005$). HS treatment in gr.6 increased abdominal hemorrhage, MAP fell to 21.2 torr ($p<.005$) with a mortality of 66% ($p<.01$). Inflation of MAST before HS during UH led to a rise in MAP to 75 torr ($p<.001$) with no mortality. It is concluded that HS leads to increased blood loss, fall in MAP and early mortality in uncontrolled hemorrhagic shock. Inflation of MAST before HS infusion prevents the fall in blood pressure and early mortality.

72 APPLICATION OF MILITARY ANTI-SHOCK TROUSERS (MAST) IN COMPENSATORY AND DECOMPENSATORY HEMORRHAGIC HYPOTENSION. Gerald Johnson III and Robert F. Bond. Oral Roberts University School of Medicine Department of Physiology, Tulsa, OK 74171.

The compensatory cardiovascular response to hemorrhage includes a baroreceptor induced activation of the sympathetic nervous system resulting in an attempt to reestablish MAP through peripheral vasoconstriction. If the hypotension is not reversed this compensatory vasoconstriction will progress to a loss of vascular tone known as vascular decompensation. The primary purpose of the present study was to compare the effectiveness of MAST applied during the compensatory and decompensatory stages of hemorrhagic hypotension. MAST pressures of 30, 50, 70 and 90 mmHg were applied during control, compensation and decompensation. The results showed that: 1) MAST pressures up to 90 mmHg were ineffective at raising MAP when applied to normotensive dogs; 2) MAP increased 62% when MAST are applied during compensation as the result of a significant augmentation of cardiac output (SV and HR) with no change in TPR; and 3) a modest increase in MAP from 40 to 55 mmHg occurred when MAST pressure was increased to 70 mmHg during compensation which was accounted for entirely on the basis of an increased TPR with no significant change in CO.
Supported in part by funds from American Heart Association, Oklahoma Affiliate.

73 COMBINED TREATMENT OF HEMORRHAGIC SHOCK BY MAST AND HYPERTONIC SALINE. EH. Landau*, D. Gross*, A. Assalia*, MM. Krausz, Hadassah University Hospital, Jerusalem, Israel, 91120.

The use of MAST (Military Antishock Trausers) in hemorrhagic shock is controversial because of a variable response in cardiac output, oliguria and metabolic acidosis. 23 awake sheep were devided into 4 groups : gr.1 (n=5)- hemorrhagic shock induced by arterial bleeding of 40ml/Kg treated by 5ml/Kg NaCl 0.9%, gr.2 (n=6)-hemorrhagic shock treated with 5ml/Kg NaCl 7.5%, gr.3 (n=5)-hemorrhagic shock treated by MAST (Jobst) inflated to 40 mmHg and 5 ml/Kg NaCl 0.9%. gr.4 (n=7)-hemorrhagic shock treated by MAST and 5ml/Kg NaCl 7.5%. Arterial bleeding led to a fall in MAP from 95 to 45 torr, CVP from 4.5 to 0.5 torr, cardiac index (CI) from 184 to 68 ml/min/Kg, urine flow (UF) from 102 to 24 ml/hr, Base excess (BE) from 0.1 to -5.7, and systemic vascular resistance (SVR) increased from 1649 to 3484 dynes.sec.cm-5. Inflation of MAST in gr.3 increased MAP to 88.7 torr ($p<.001$), CVP to 4.7 torr ($p<.001$), CI to 79 ml/min/Kg, UF to 34 ml/hr, BE to -4.1 and SVR to 3714 ($p<.001$). Infusion of NaCl 7.5% in gr.4 led to rise in MAP to 98.3 torr ($p<.001$), CVP to 10.8 torr ($P<.01$), CI to 174 ml/min/Kg ($p<.001$) which was significantly different from gr.3 ($p<.01$), UF to 125 ml/hr ($p<.001$), BE fell to -0.4 ($p<.01$) and SVR to 1819 dynes.sec.cm-5 ($p<.001$). It is concluded that treatment of hemorrhagic shock by MAST and hypertonic saline consistantly increases CI, reduces SVR, and thus improves urine output and metabolic acidosis.

74 A CHANGE IN CONJUNCTIVAL OXYGEN TENSION IN HEMORRHAGIC SHOCK. Y. Kikuta, O. Moritsune, S. Tezuka, H. Kawabata and K. Okada. Teikyo University, Itabashi, Tokyo 173 Japan.

Conjunctival PO_2 ($PcjO_2$) had been evaluated as an early warning device of cardiopulmonary compromise. This study was undertaken to investigate a change in $PcjO_2$ during hemorrhagic shock, and to evaluate a relationship between $PcjO_2$ and other parameters (carotid blood flow or blood pressure). Adult mongrel dogs were anesthetized with N_2O-O_2-enflurane, and were ventilated with a constant volume ventilator. Both femoral arteries were cannulated to measure blood pressure and to exsanguinate. A $PcjO_2$ sensor was placed under the eyelid. A blood flow probe was placed around the carotid artery to measure carotid blood flow. Cerebral regional blood flow was determined by the hydrogen clearance method and cerebral tissue PO_2 was measured by a fine Clark type needle. Soon after bleeding, carotid blood flow was decreased to 1/3 or 1/6 from control level, whereas $PcjO_2$ was decreased to 1/10 of control. After retransfusion both carotid blood flow and $PcjO_2$ were returned to control or exceeded above control. However both cerebral tissue PO_2 and cerebral regional blood flow did not correlate well with $PcjO_2$. The development of continuous monitors that detect deterioration in oxygen transport represents a significant advance in shock. Since in this study FiO_2 was kept constant and ventilation was not changed, it was suggested that the $PcjO_2$ change was induced mainly by the change of carotid blood flow. In conclusion, $PcjO_2$ will be a reliable parameter for monitoring shock status.

75 FLUOSOL^{R}-DA PROLONGS SURVIVAL OF RATS AFTER FATAL HEMORRHAGE. S. McCoy, R.K. Spence,* R.C. Camishion,* Departments of Surgery, UMDNJ-Robert Wood Johnson Medical School at Camden, Cooper Hospital/University Medical Center, Camden, N.J. and East Tennessee State University College of Medicine, Johnson City, TN 37614.

Clinical trials of the fluorocarbon blood substitute Fluosol-DA,^{R} 20% (FDA) have failed to show significant benefit because of the diversity of the patient population and entry criterion based on hemoglobin concentration alone. The present study was designed to test the efficacy of FDA for resuscitation in a standard model of acute hemorrhage. Sprague-Dawley SPF male rats were subjected to a modified Wiggers model of hemorrhagic shock at a mean arterial blood pressure (MABP) of 40 mm Hg. When a rat attained irreversible shock (IS) by requiring reinfusion of 10% of its shed blood to maintain MABP, it was resuscitated in either room air or an O_2 tent by infusion of a test solution (volume equal to shed blood volume). Survival time was recorded between IS and death. Rats treated with shed blood (4 rats), blood + O_2 (7), hetastarch (6), hetastarch + O_2 (10), or FDA + O_2 (10) did not differ significantly with respect to weight (315.7 ± 30.7g), baseline MABP (73.0 ± 3.6 mm Hg), time to IS 105.5 ± 9.5 min, or maximum volume shed (1.8 ± 0.4% body weight). The FDA + O_2 group survived 221.9 ± 30.8 min after IS; all others averaged 129.05 ± 30.8 min ($p<.0001$).

Resuscitation with FDA at high FiO_2 nearly doubled survival time of rats subjected to a standard model of hypovolemic shock as compared to conventional therapies. Volume resuscitation after acute hemorrhage with FDA and O_2 may offer advantages over current protocols in humans as well.

76 EFFECT OF FASTING ON THE BLOOD FLOW DISTRIBUTION RESPONSE TO SEVERE BLOOD LOSS. F.J. Pearce and W.R. Drucker Univ. of Rochester, Rochester, NY 14642.

Fasted animals, when well hydrated and studied using an isobaric pressure model of hemorrhagic shock, show comparable compensatory capacities but they decompensate at a much more rapid rate. Depleted glucose reserves has been proposed to be important to the inability of an animal to maintain its homeostatic efforts, however, differences in blood flow distribution may also play a role. The present study explored this latter possibility by measuring the distribution of blood flow at identical fractions of the projected maximal shed blood volume (MSBV) using an isobaric pressure model. Rats were either fed or fasted (n=5) for 24 hrs (n=6), anesthestized and bled to a MABP of 40 mmHg over 10' and maintained there until death. Organ blood flows were determined during the control period (I) at 50% (II) and 100% (III) of the MSBV and after return of 20% (IV) and 75% (V) of the MSBV using the microsphere reference sample method. Only 2 of the 5 fasted animals lived to period V. Before hemorrhage, fasted rats showed a 3-fold greater adipose tissue flow and a 2-fold greater hepatic arterial flow (HAF). During period II, adipose tissue and HAF was greater in fasted rats but these differences disappeared by period III. Skeletal muscle flow was lower in fasted rats during period III but returned to control levels or higher during decompensation (periods IV & V). The data indicate no differences in blood flow to the vital organs, the heart and the brain, that might explain the faster deterioration of fasted animals. The loss of vascular tone during decompensation appeared primarily in the splanchnic and skeletal muscle beds and occurred earlier and faster in fasted animals. Plasma glucose may be important to maintenance of vascular tone in these beds. Supported by NIH grant #GM30095.

77 RESUSCITATION OF HEMORRHAGE (43 ML/KG) USING LESS THAN 1 ML/KG OF SATURATED NaCl/ DEXTRAN SOLUTION. PR Perron*, JC Walsh*, RA Gunther, JW Holcroft and GC Kramer, Depts. of Human Physiol. and Surgery, Sch. Med., Univ. of Calif., Davis, CA 95616.

Successful resuscitation of hemorrhage can be accomplished with small volumes (4 ml/kg) of hypertonic/hyperoncotic solution, 7.5% NaCl/6% dextran 70 (Dx), J Surg Res 39:517. The present study evaluated the safety and effectiveness of smaller volumes (< 1 ml/kg) of a more concentrated solution of saturated 30% NaCl/24% Dx (Group 1) compared with 7.5% NaCl/6% Dx (Group 2). Adult conscious sheep, 41-48 kg, were bled to maintain mean arterial pressure (MAP) at 50 mmHg for 2 hours; mean bled volume = 34 ml/kg. Sheep were then given a 40 ml bolus infusion of one test solution; additional boluses were given if MAP fell below 70 mm Hg. Both solutions caused rapid increases in MAP and cardiac output (CO) with the response of 30% NaCl/ 24% Dx being significantly better than 7.5% NaCl/6% Dx at 3 and 15 minutes after infusion. Over a 3 hr period only 1 bolus of 30% NaCl/24% Dx was required to maintain MAP > 70 mm Hg (n = 4) compared to a mean of 2.5 boluses of 7.5% NaCl/6% Dx (n = 4). Table shows MAP and CO during baseline (BL), after 2 hrs of hemorrhage (Hem), and after one 40 ml bolus of 30% NaCl/24% Dx, Group 1.

	BL	Hem	15 min	1 hr	2 hr	3 hr
MAP mm Hg	94	50	98	87	81	80
CO l/min	4.8	2.3	5.5	4.2	5.3	4.1

No deleterious effects were observed with measured serum sodium increases to 160-170 mEq/L. The effectiveness of hypertonic/hyperoncotic resuscitation may be dependent on total solute load. (Supported by DOD contract DAMD 17-86-C6115, and NIH HL18010.)

78 COMPARATIVE HEMODYNAMIC EFFECTS OF BLOOD RETRANSFUSION AND LOW MOLECULAR WEIGHT DEXTRAN (ISODEX) ADMINISTRATION IN SEVERE HEMORRHAGIC SHOCK.-M.A.Saragoça;M.P.S.G.Amorim;A.M.A.Bessa;M.L.Cezaretti;S.A.Draibe;O.L.Ramos (Spon:M.R.Silva).-Nephrology Division. Escola Paulista de Medicina. São Paulo, SP,Brazil.

In dogs submitted to severe hemorrhagic shock, we compared the hemodynamic responses to total retransfusion of whole blood (WB) or infusion of equal volumes of a 3% solution of Dextran, MW-40.000 (D40). Shock was induced in dogs by controlled bleeding (40 ml/Kg, over 1 hour)and then 3 infusions of 1/3 of the shed blood or equal volumes of D40 were administered. After each infusion we determined Cardiac Index(CI), mean arterial pressure and derived indices and also, Pulmonary Wedge Pressure(PWP). CI decreased in both groups with shock(WB=from 3.08±0.31 to 1.10± 0.19,$p<0.001$; D40, from 2.31±0.21 to 0.63±0.11, $p<0.001$) and was restored to

control levels with D40 (2.35±0.24, ns vs control)but not with WB(1.66±0.11,p< 0.001). Stroke index was also significantly reduced with shock in both groups(WB, from 25.0±3.0 to 5.8±0.8,p<0.001 and D40, from 16.3±1.0 to 3.6±0.7, p<0.001) and was restored to control levels in D40 (14.4±1.4, ns vs control), but not WB group(10.8± 0.95,p 0.001 vs control). The final hematocrit with D40 was significantly lower than with WB(16.8±1.1 vs 39.3±2.14, p<0.001). None of the groups showed increases in PWP above control levels(WB from 11.7±1.1 to 11.2±1.8, ns; D40, from 11.2±1.0 to 12.3± 1.5,ns) We thus conclude that infusions of 3% solutions of Dextran are more effective than whole blood transfusions in restoring the hemodynamic abnormalities in the acute treatment of severe hemorrhagic shock and that this difference may be attributed to more favourable rheological properties of the blood.

79 COMPARISON OF ANTISHOCK EFFECT AND LYSOSOMAL STABILIZATION ACTION OF ANISODAMINE WITH DEXAMETHASONE. J-Y Su*, L-L Wu*and Z Song* (Spon:M-S Liu). Beijing Med. Univ., Beijing, PR China.

Anisodamine (654-2) has been proved to be an effective antishock drug in China. This work compared its antishock effect with dexamethasone (Dex) on a standardized cat hemorrhagic shock model. 654-2 5mg/kg or Dex 5mg/kg in 5ml saline were dripped i.v. when MABP was bled to 40 mmHg and maintained at that level for 3h, then the shed blood was reinfused. At the end of 2h after reinfusion, MABP of the control group (n=6, infuse 5ml saline during oligemia) was 57.5±9.5 mmHg, while in 654-2 group (n=6) was 127.7±4.6 mmHg (P<0.01), and in Dex treated group (n=5) was 82.0±18.6 mmHg (P<0.05). It seems that 654-2 might keep an higher MABP than Dex (P<0.05) during shock therapy. Plasma cathepsin D (CD) activity increased from below 6 U/mg. Pr. before hemorrhage to 54.95± 5.9 U/mg.Pr. after 3h of oligemia in the control group, while at the same time in 654-2 group and Dex group plasma CD was 20.9±4.3 U/mg.Pr. (P<0.01) and 33.1 ±5.9 U/mg.Pr. (P<0.01). Both 654-2 and Dex significantly blunted the increase of plasma CD. At the end of experiments pancreas and intestinal mucosa were excised quickly, free and bound CD were determined respectively. Data showed that 654-2 and Dex both inhibited the release of pancreatic lysosomal CD, but on the intestinal mucosa, 654-2 exerted much better protection action than Dex. Results showed that 654-2 exerts a comparatively better antishock action in hemodynamic aspect, and its special stabilization action on intestinal mucosal cell lysosomes deserves attention.

80 DOES BEING FEMALE DECREASE THE MORTALITY FROM MAJOR THERMAL INJURY IN CHILDREN. R. Barrow*, D. Herndon, T. Rutan,* M. Desai. UT Med Br and Shriners Brns Inst, Galveston, TX, 77550.

The effect of sex on mortality was evaluated in 251 children admitted between 1981 and 1986 with greater than 30% total body surface area burned (TBSAB) and no related inhalation injury. All were treated within 72 hours of burn injury with complete excision of all full-thickness burns with immediate application of widely expanded auto graft and cadaver skin as necessary. The patients were 0-18 years of age with an overall mortality of 8.8%. There was a 1.5% mortality rate in the population of children with 30-50% TBSAB (n=136) and a 17% mortality rate in the 50-100% TBSAB (n=115) population. The children were divided into male (M) and female (F) groups with 30-50% TBSAB (M; n=77, F; n=59) and groups with 50-100% TBSAB (M; n=70, F; n=45). Age and % TBSAB were compared using the unpaired t-test. Mortality rates were compared using the chi-square test of independence with the Yates correction. Values are MEANS ± SEM. Between male groups, *=p<0.001

	30-50% TBSAB				50-100% TBSAB			
BURN ONLY	n	age-yrs	%TBSAB	%Mortal.	n	age-yrs	%TBSAB	%Mortal.
Males	77	8.1±0.6	37±0.5	1.1*	70	7.2±0.6	70±1.8	21.4*
Females	59	6.2±0.7	37±0.8	1.7	45	6.3±0.9	65±2.1	11.1

A significant increase in mortality accompanies increasing burn size in male children, however, this increase does not occur in the comparable female group indicating that being female in some way decreases mortality from major thermal injury in children.

81 SMOKE INHALATION WITH BURNS - A LETHAL COMBINATION, David Blinn,* Harvey Slater, I. William Goldfarb. The Western Pennsylvania Hospital Burn/Trauma Center, Pittsburgh, PA 15224.

Smoke inhalation is known to add significant morbidity and risk of death to patients with burns. Estimating the severity and course of an inhalation injury is difficult as clinical and pathophysiologic signs may occur hours or days after the injury. In response to requests for guidelines for referral and initial management of patients with burns and smoke inhalation, we have reviewed all such patients admitted to this facility over the past 24 months. Of the 86 patients in this study group, there were 33 survivors (38.4%) and 53 deaths (61.6%). The mean age was 45 years with a range of 2-94 years. 76 patients required endotracheal intubation (88.4%). The mean total body surface area burn was 46.5%; range 0-100%. Admission chest x-rays were normal in 91% of the patients. Chest auscultation was normal in 91% of the patients. The mean PAO_2 upon admission in the 86 patients was 155 mmHg with a range of 39-310. Admission PAO_2 was not predictive of outcome. We categorized inhalation injury as mild, moderate, or severe based upon physical findings and bronchoscopy. Initial evaluation of patients with smoke inhalation and burns using parameters of chest auscultation, chest x-ray and arterial blood gases were found to be unreliable predictors of subsequent respiratory failure and survival. Fatal outcome correlates with evidence of severe smoke inhalation, age, total burn surface area, and moderate or severe facial burns. Patient with even >15% of the TBSA have a significant risk of respiratory failure.

82 PULMONARY VASCULAR REACTIVITY IN THERMAL INJURY. William Cioffi*, James DeMeules, Richard Gamelli*. University of Vermont, Dept. of Surgery, Burlington, VT 05405

The effects of thermal injury on pulmonary vascular reactivity (PVR) is unknown. Male, Sprague-Dawley rats received a sham burn (S) or a 30% full-thickness scald injury (B). 18 hours after injury main pulmonary arteries (PA) were removed and tension dose response curves to norepinephrine (NE), prostaglandin ($PGF_{2\alpha}$), serotonin (5-HT), bradykinin (BKN) and potassium (K^+) were obtained. PA's from burned animals showed a reduction in peak tension development to all agonists. Some burned animals were resuscitated (R) with Ringer's lactate 15 cc/180 gm body weight IP prior to burning. PA's from R demonstrated partial reversal of the defect. To rule out hypovolemia as a cause, the experiment was repeated using PA's from group H sustaining a 25% blood volume loss without R. PA's from H were no different than S. We conclude that the decreased PVR is burn specific and not resolved by fluid administration. Thermal injury may cause a depolarization of vessels altering voltage dependent calcium channels resulting in subnormal K^+ induced contractions in B and R when compared to S. Contraction dependent upon receptor mediated calcium channels (i.e., NE < 10^{-7}M) was no different between S, B, R or H.

	Maximal Tension Development gm ± SD (N)				* p<.05 compared to S.	
	NE	$PGF_{2\alpha}$	5 HT	BKN	K^+	
S	1.66±0.5 (10)	1.34±0.3 (10)	0.76±0.2 (11)	1.25±0.4 (9)	1.66±0.4 (4)	
B	1.29±0.3 (8)*	0.87±0.3 (10)*	0.41±0.1 (6)*	0.59±0.1 (9)*	0.61±0.2 (9)*	
R	1.41±0.4 (12)	1.01±0.3 (8)	0.99±0.8 (6)	0.64±0.2 (13)*	0.93±0.3 (9)*	
H	2.06±0.9 (5)	1.32±0.4 (6)	0.99±0.3 (5)	0.97±0.36 (8)		

83 EFFECTS OF VERAPAMIL ON MYOCARDIAL CONTRACTILITY IN HEARTS OBTAINED FROM BURNED GUINEA PIGS (GPs). S.T. Conahan*, M.E. Giamo* and H.I Miller. LSU Medical Center, New Orleans, LA. 70112.

Previous studies have demonstrated reduced myocardial function in hearts obtained from extensively burned GPs. Since myocardial contraction in the GP and man is heavily dependant upon the influx of extracellular calcium through slow calcium channels, we examined the effect of the calcium slow channel blocker, verapamil, on aortic peak systolic pressure (APSP), left ventricular peak systolic pressure (LVPSP), dP/dt and -dP/dt in hearts obtained from GPs in burn shock. GPs weighing 300-500 grams were deeply anesthetized with enflurane, shaved, and burned (3rd degree, 40% body surface area), by immersion in boiling water. Non-burned GPs served as controls. 4 hrs later, hearts were quickly excised and prefused on a working heart apparatus at a filling pressure of 12.5 cm H_2O. Following stabilization, verapamil was added to the prefusion system to yeild final concentrations of 1×10^{-8}, 2.5×10^{-8}, 5×10^{-8}, 1×10^{-7}, and 2×10^{-7} mM. In control hearts, verapamil

produced a dose dependant reduction in +dP/dt raging from 8% to 61%. In contrast, no significant effects were seen in the burn hearts until verapamil concentration was greater than 5×10^{-8} mM. EC_{50} values for control and burned hearts were 6.7×10^{-8} and 2.4×10^{-7} respectively ($p<0.05$). Similar results were obtained when LVPSP and APSP were examined. These differences suggest that an abnormality may exist in the slow calcium channel in hearts of burned GPs.

84 SPINAL SHOCK: THE EARLY HEMODYNAMIC MANIFESTATIONS IN ACUTE CERVICAL CORD INJURY. T. Fabian, G. Burruss, G. Stanford, L. Payne, R. Patterson University of Tennessee, Memphis, TN 38163

"Spinal shock" is commonly employed to suggest a state of circulatory shock in addition to the originally defined neurologic sequelae of spinal cord injury. In fact, the hemodynamic characteristics of patients with acute cervical spine injuries are poorly defined. We employed invasive monitoring methods in six patients during the first 72 hours following cervical cord transection for serial determination of systemic pressure, cardiac output and cardiac filling pressures. Other parameters were subsequently calculated.

Time (hrs)	8	16	24	32	40	48	56	64	72
HR	67	75	71	67	66	73	73	70	70
MAP	81	75	73	76	73	74	82	83	80
CI	4.9	4.9	5.0	4.4	3.4	4.8	5.5	4.?	4.3
SVR	593	535	593	717	716	631	582	734	[illegible]
PCWP	9.8	9.0	9.8	11.7	13.5	14.6	16.3	12.8	12.0
FLUIDS	2348	656	356	372	428	359	405	403	326

Acute cervical cord transection in humans results in systemic hypotension accompanied by a paradoxical bradycardia, presumably due to unopposed vagal activity. Furthermore, there is an apparent interruption of the Bainbridge reflex. Cardiac output is maintained at supra-normal levels in these patients, however, indicating that ventricular contractility is not inhibited by such injuries in humans, as opposed to the results in animal studies. There are significant implications for the clinical management of "spinal shock".

85 LUNG MICROVASCULAR LESIONS WITH AND WITHOUT SMOKE INHALATION IN THERMALLY INJURED SHEEP. D. Herndon, L. Traber,* M. Brown,* D. Traber, R. Barrow.* UT Med Br and Shriners Brns Inst, Galveston, TX, 77550.

Mortality in patients with thermal injuries and smoke inhalation is greater than with either injury alone. We studied inhalation injury in sheep with and without dermal burns. Two groups of six sheep each were insufflated with smoke from smoldering cotton. In addition one group received a third-degree dermal burn covering 40% total body surface area. All animals were under anesthesia during smoke and thermal exposures. Lung lymph flow (LQ) increased in both groups but was higher in the animals receiving only smoke injury. Cardiac index and lymph to plasma protein ratios showed no change from control while pulmonary artery pressures increased in both groups by the same amount.

		Lung Lymph Flow in ml/hr Postinjury (hrs)			
Group	N	0	24	48	72
Smoke	6	7.4±1.1	35.5±10.4*	26.4±7.1	22.7±5.2
Smoke-Burn	6	7.8±1.6	17.5±4.1	21.1±6.3	24.4±9.1
Sham Control	6	8.7±1.2	8.1±1.5	8.2±1.8	8.9±1.7

Values expressed as Mean±SEM, *$p<0.05$ smoke vs. smoke burn

Injury to the microvasculature of the lung with smoke inhalation is attenuated when there is a concomitant thermal injury to the skin which may explain the delay in pulmonary edema observed in burned patients with simultaneous smoke inhalation.

NIH Grant #GM33324

86 EARLY PLASMA LIPID PEROXIDES, CONJUGATED DIENES AND ESTIMATED SUPEROXIDE RADICAL PRODUCTION FROM THE NEUTROPHIL IN PATIENTS FOLLOWING MAJOR BLUNT TRAUMA. N. KHAN, M. GIROTTI, P. WALKER, A. ROMASCHIN, B. McCLELLAN. Dept. of Surgery, University of Toronto, Toronto, Canada.

Membrane permeability changes are known to occur following major blunt trauma in man. Superoxide radical (O_2^-) production from activated neutophils (PMN) interacting with membrane polyunsaturated fatty acids might result in permeability alterations and be evidenced by elevated plasma peroxidized lipids. Plasma from 12 adult patients with major blunt trauma (ISS>16) within 2-4 hours of injury were studied. Patients were hemodynamically stable and had not

received any medications. Lipid peroxide products (LP) were measured using the thiobarbituric acid/malondialdehyde technique. Conjugated dienes (CD) were measured by spectrophotometric analysis of lipid residue after chloroform ethanol extraction. PMN production of O_2^- was estimated by incubation of normal PMNs from healthy human volunteers with the trauma plasma, followed by the superoxide dismutase inhibitable NADPH reduction of cytochrome C after FMLP stimulation. The table summarizes our results.

	LP(nmol/ml)	CD(nmol/ml)	O_2^-(nmols/2x106 PMN)	
Control	10.3±1.5	38.5±5.6	2.73 ± .40	*p<0.05
Trauma	8.8±2.6	44.5±19.1	2.27 ± .63*	paired T-test

We conclude that in early trauma, there is no elevation in plasma lipid peroxides but, there does appear to be a plasma associated factor capable of reducing normal PMN production of O_2^-.

87 EVIDENCE OF LOCAL COMPLEMENT ACTIVATION IN CUTANEOUS THERMAL INJURY IN RATS. Keith T. Oldham, Karen S. Guice, Gerd O. Till, Peter A. Ward, The University of Michigan School of Medicine, Ann Arbor, MI 48109.

Systemic complement activation occurs with cutaneous thermal injury but the site and the mechanism of this event have not been clearly demonstrated. The purpose of this study was to establish whether complement activation occurs locally at the site of a burn wound. METHODS: Anesthetized 350 gram male Long Evans rats were prepared by intrarenal inferior vena cava (IVC) ligation. The rats were then given a 25-30% total body surface area thermal burn by immersion of the hindquarters in a 70°C water bath for 30 seconds. Thirty minutes after burn, selective sampling of the hindquarters venous effluent (IVC) and systemic right atrial (RA) venous blood was done. Serum chemotactic activity was measured. RESULTS:

	RA	IVC
IVC ligation alone (n=10)	36.1 ± 4.3 μm	37.9 ± 6.0 μm
IVC ligation + burn (n=12)	55.0 ± 7.6 μm	113.8 ± 12.7 μm*

*p<0.002

Antibody to C5a eliminated the chemotactic activity found in the IVC sera from burned rats. CONCLUSION: Thermal injury of skin causes local activation of complement and appearance in serum of C5a chemotactic activity.

88 COMPARISON OF DEGREES OF INHALATION INJURY. R. Kimura*, L. Traber*, D. Herndon, H. Linares, D. Traber. UT Med Br & Shriners Brns Inst, Galveston, TX, 77550.

The inhalation of smoke produces changes in the lung microvasculature. This study was accomplished to determine if these changes are related to the quantity of smoke inhaled. METHODS: Sheep (N=18) prepared with chronic lung lymph, extravascular lung water (EVLW), Swan-Ganz and left atrium catheters one week before study received three different degrees of inhalation injury (8x4, 12x4 and 16x4 breathes of smoke). The COHb levels were 71±7 and 92±3 for the low (L) and high (H) injury groups respectively. Immediately after injury, variables were measured for 48 hrs. The sheep were sacrificed and their lungs removed for wet to dry lung weight (W/D) measurements and microscopic study. RESULTS: The pulmonary changes were recognizable as dose dependent lesions microscopically. The increased lung lymph flow (LQ) and protein clearance (PI) were directly proportional to the amounts of smoke inhaled. Extravascular lung water was 336±43 ml for L and 537±68 ml for H at 48 hrs. The decreased P:F ratio (PaO2/FiO2) was observed in group H only. Hemodynamics were not statistically different between groups. CONCLUSION: Smoke inhalation results in a dose related injury which can be reproduced in our ovine lung lymph model. (Supported by NIH Grant #GM33324)

GROUP	LQ	PI	W/D	PAP	P:F
8x4(L)	12±2	6±1	6.5±0.6	22±1	367±19
12x4(M)	26±7*	14±4	8.3±3.0	23±2	365±20
16x4(H)	49±8*+	30±5*+	11.6±0.6*	23±1	251±43*+

DATA are Mean±SEM at 48 hrs. *=p<0.05 vs 8x4 +=p<0.05 vs 12x4

89 HYPOTENSION, SPLANCHNIC HYPOXIA AND ARTERIAL ACIDOSIS IN ICU PATIENTS.
R. Fiddian-Green. University of Massachusetts Med. Ctr. Worcester, MA 01605

Transient episodes of mucosal ischemia permit the absorbtion of bacteria, bacterial toxins and products of ischemic mucosa into the circulation of animals and thereby cause myocardial depression and irreversible shock. Transient episodes of gastric mucosal ischemia, evident from the development of intramucosal acidosis, occur in 50% of patients undergoing cardiac surgery. Complications of surgery were best predicted from the development of hypotenstion, intramucosal acidosis and acidosis in arterial blood. We have measured the systolic blood pressure (SBP), pH in the gastric mucosa (pHi) and pH in arterial blood (pHa) randomly on 323 different days in 60 patients in intensive care units. All were receiving antacids and/or cimetidine. The severity of their illness, measured on a scale of 0 to 5, was 2.51 + 1.3 (mean + SD). A SBP < 100mmHG was evident on 8 days (2.5%) in 8 (13.3%) of patients, and a SBP < 80mmHG on 2 (0.6%) days in 2 (3.3%) of patients. Intramucosal acidosis in the stomach (pHi below 7.32, the lower statistical limit of normality in 47 patients with vascular disease) indicative of mucosal hypoxia was evident on 229 days (71%) in 43 (72%) of the patients studied. Acidosis in arterial blood (pHa < 7.36) was evident on 10 days (3.1%)in 5 (8.3%) of the patients. It is concluded that transient episodes of hypotension and arterial acidosis are effectively prevented in patients being treated in intensive care units but that splanchnic hypoxia is not being recognized and not being prevented. The management of patients might be improved by monitoring the intramucosal pH in the stomach and preventing intramucosal acidosis by improving the adequacy of splanchnic oxygenation.

90 PLASMA AND DATA COLLECTION IN A MULTICENTER STUDY RELATED TO MEDIATORS OF MULTI ORGAN FAILURE.
R. Kneidinger, I. Jung, H. Redl, G. Schlag. Ludwig Boltzmann Institute for Experimental Traumatology, Vienna, A-1200, Austria

To study different potential mediators of sepsis-related organ failure various types of blood samples must be obtained. To minimize specimen loss, a color code system is used. This starts with color-coded blood specimen collection tubes,in which the different inhibitors are prepacked per patient/ per sampling event. Parallel color-coded mini-vials (max. 1 ml) in transport racks (Makrowell system) were chosen for plasma storage. The transport racks (per patients) are distributed into similar racks (per type of analysis) after arrival in the laboratory to facilitate further plasma processing. At the same time corresponding files are created in a personal computer (PC) using advanced spread-sheet computing. From these sample statistics are calculated and worksheets are prepared.

Parallel to the samples, clinical data are collected in patient`s "log books", which correspond to several spread sheet files in the personal computer. After entering the data, derived parameters of e.g. gas exchanges and kidney status will be calculated and finally data will be automatically combined to yield several "scores", such as APACHE II or MOF score.

Finally, both clinical and biochemical data will be combined and transferred to a main frame computer via modem and further analyzed using the SAS software package.

91 QUANTITATIVE ASSESSMENT AND SIGNIFICANCE OF INTRAOPERATIVE STRESS IN HEPATECTOMY.
K.Ozawa* Y.Shimahara,* S.Wakashiro* I.Ikai,* Y.Yamaoka,* N.Kobayashi* K.Mori* Y.Kamiyama. Department of Surgery, Kyoto University School of Medicine. Kyoto, Japan.

Decrease in blood ketone body ratio (KBR:acetoacetate/3-hydroxybutyrate), which reflects hepatic mitochondrial redox potential, is associated with occurrence of multiple organ failure after surgery. In this study, intraoperative stress in hepatectomy was determined by a serial measurement of KBR during operation and analyzed in relation to postoperative complications. In the control cases (cholecystectomy, gastrectomy, etc.), the KBR was maintained at over 0.7 throughout and after operation with no postoperative complication. In hepatectomized cases, however, the KBR decreases to under 0.7 during operation, when hepatic vascular occlusion, rotation of hepatic robes, dissection of hepatic hilus and hepatic resection were performed. In 13 cases (Group A) out of 23 hepatectomies, the decreased KBR was restored immediately to over 0.7 when the causative maneuvers were terminated, while in other 10 cases (Group B), it remained under 0.7. In Group A,

the postoperative KBR showed over 0.7 and complication was seen in only one case (8%). By contrast in Group B, it showed 0.7-0.4 transiently, in which periods more than one complications such as encephalopathy, GI bleeding, DIC were seen in 80% of the patients. In conclusions, an intraoperative stress in hepatectomy can be quantified by measuring KBR. A prolonged decrease in the KBR during hepatectomy is associated with depression of postoperative KBR and high incidence of complications.

92 SIGNIFICANCE OF DECREASED BLOOD KETONE BODY RATIO (KBR) IN THE OCCURRENCE OF MULTIPLE ORGAN FAILURE (MOF) AFTER SURGERY. Y.Shimahara, I.Ikai, S.Wakashiro, Y.Tokunaga, T.Nakatani, Y.Kamiyama, K.Ozawa. Department of Surgery, Kyoto University School of Medicine. 54 Kawaracho, Shogoin, Sakyoku, Kyoto, Japan

Postoperative MOF was studied in relation to the changes in KBR (acetoacetate/3-hydroxybutyrate) which reflects hepatic mitochondrial redox potential. Six hundred and fifty cases of abdominal surgery including hepatectomy were analyzed. Changes in postoperative KBR were classified into 4 groups: A (>0.7), B (0.7-0.4), C (0.4-0.25), D (<0.25). In Group A (520cases), no MOF was seen. In Group B(98cases), one or two organ failures were observed transiently. All of the patients of groups A and B survived. In Group C (32cases), however, MOF developed in all patients and only 6 cases (10.1%) survived. Out of 32 cases of Group C, 26 patients shifted to Group D and died. Numbers and incidences (%) of failured organs in Group C patients are indicated as follows along with the decrease in the KBR.

KBR	Failured ograns	Lung	Liver	kidney	Brain	GItract	Heart	others
>0.7	0-I	5	20					
0.7-0.4	0-II	28	51	31	10	10	3	5
0.4-0.25	III-VI	33	83	56	63	33	6	40
<0.25	IV-VII	70	97	84	84	35	59	73

In conclusion, the decrease in KBR is strongly linked with an occurrence of MOF in the postoperative courses. Thus, it was suggested that the derangement of hepatic mitochondrial function is associated with a precipitation of MOF probablly by inducing a metabolic abnormalities of the whole body.

93 THE CHANGES IN THE ARTERIAL REDOX POTENTIAL, LACTATE AND BASE EXCESS OF THE PATIENTS IN HEMORRHAGIC SHOCK S.Taniguchi*, J.Yoshitake* (Spon: Japanese Shock Society) Dept. of Anesthesiology, Faculty of Medicine, Kyushu University, Fukuoka, 812, Japan

The clinical study was performed in 9 patients received more than 6000 mL of blood transfusion for the treatment of shock. 5 patients out of 9 were successfully treated with surgical interventions, 2 were expired in the end of the operation and 2 were lost in a few days after admission in ICU. pH and rH_2 of blood obtained from these patients were measured with B.E.-VINCENT apparatus, and redox potential(E) was calculated from these data. Simultaneously serum electrolytes, arterial blood gases, blood sugar and lactate were measured. The changes in the mean arterial E, lactate and B.E. in the survivals and non-survivals were shown in table. Lactic acidosis was more serious in the non-survival group than in the survival group preoperatively. In the non-survival group, lactic acidosis was improving during surgery and further improvement was seen after admission in ICU, nevertheless the patients were expired shortly. The E values of the survivals were maintained at somewhat higher levels than its normal value, that is 240 mV, during surgery. On the other hand those of the non-survivals consistently decreased in their processes. It is concluded that arterial E value is more useful than the severity of lactic acidosis in estimating the outcomes of hemorrhagic patients.

	survival		non-survival		
	pre	post	pre	post	in ICU
E (mV)	254.4	272.6	243.3	222.0	216.5
lactate(mg/dL)	15.8	32.1	110.6	98.5	57.1
B.E.(mEq/L)	2.26	4.84	-12.0	-5.9	-1.2

94 **THERMODILUTION RIGHT VENTRICULAR EJECTION FRACTION (RVEF) IN SEPTIC SHOCK PATIENTS.** J.L.Vincent, C.Reuse and B.Contempre Dept of Intensive Care, Erasme University Hospital 1070 Brussels, Belgium.

Thermodilution RVEF was measured in 56 consecutive septic patients (fever or leukocytosis associated with a source of sepsis or bacteremia) and in non-septic "control" patients without sepsis or cardiopulmonary impairment. Each patient was monitored with a modified Swan-Ganz catheter (93A-431H-7.5F,Edwards Lab.) equipped with a fast response (50 msec) thermistor, a modified proximal port (3 hole, 21 cm from tip) and intracardiac ECG electrodes. RVEF was computerized (prototype REF1)

from the thermodilution curve using an algorithm based on exponential curves analysis. Of 273 measurements, 93 were obtained during septic shock (hypotension and lactacidema)(SS),118 in sepsis without shock (S),and 62 in control patients (C). RVEF was 23.8±8.2% in SS, 30.3±10.1% in S and 32.5±7.1% in C. Differences were significant between SS and S or C ($p<0.01$) but not between S and C. Pulmonary artery pressures were significantly higher in SS and S than C (25.6±8.0, 27.4±8.3 and 18.5±6.6 mmHg, respectively). Stroke index was lower in SS than in S or C (29.0±10.5, 37.2±13.5 and 34.3±12.5 ml, respectively). Initial RVEF in septic shock was higher in patients who ultimately survived (27.8±8.6 vs 20.9±6.7%,$p<0.02$), while the other hemodynamic parameters were not markedly different. We conclude : 1) RVEF is significantly reduced in SS but not in S. 2) RV depression in SS is essentially due to myocardial depression and pulmonary hypertension. 3) RVEF has important prognostic implications in SS. Since thermodilution RVEF can now be easily measured at the bedside, this study has immediate clinical applications.

95 A NEW PARAMETER IN THE ASSESSMENT OF SEPTIC SHOCK PATIENTS - SERUM GLUTAMATE DEHYDROGENASE. R.J. PIVON*, R.A. BROWN*, S.C. SKORYNA*, P. KOCH* and D.S. MULDER
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Dysfunction of liver mitochondria during sepsis and septic shock has frequently been demonstrated in animal models. This dysfunction has been attributed to alterations in the energy-linked respiratory processes, which occur in the mitochondria. It has been demonstrated that glutamic oxaloacetic and glutamic pyruvic transaminases are by their reactants linked to glutamate dehydrogenase in mitochondria of the liver. In the current study, Serum Glutamate Dehydrogenase (SGDH) levels were determined daily in patients, who were in sepsis, septic shock or non-septic shock, such as hypovolemic or cardiogenic. Patients undergoing major surgical procedures without post-operative complications, such as sepsis or shock, were used as control subjects. In the 10 patients with abdominal sepsis, the SGDH values ranged from 6.36 to 498.21 U/L. In 5 septic shock patients, the SGDH values ranged from 514.98 to 3839.20 U/L; while in 3 non-septic shock patients, the values ranged from 6.68 to 26.75 U/L. In the control group, the SGDH values were within the notmal range of 1.00 to 4.68 U/L, indicating that the operative procedures have no influence on the levels of SGDH. It is suggested that SGDH determinations may be a valuable adjunct in the differential diagnosis of septic shock. Follow-up studies of these patients may reveal that SGDH might also be useful as a prognostic indicator as well.

96 PLASMA OSMOLALITY GAP (OG) AS THE CELLULAR INJURY SCORE IN MULTIPLE ORGAN FAILURE (MOF) PATINETS. H. Hirasawa, T. Sugai*, H. Inaba* and M. Ohkawa. Chiba Univ. School of Medicine, Chiba, Japan 280.

It has been claimed that an index to evaluate the cellular injury is necessary to improve the management of the MOF patients since the pathogenesis of the MOF could be the summation of the cellular injury in various failed organs. The present study was undertaken to investigate whether the OG could be a cellular injury score in the MOF patients. The OG, defined as the difference between the measured plasma osmolality and the predicted plasma osmolality calculated from plasma Na, urea nitrogen, glucose and water, was studied in 35 MOF patients during ICU stay. Plasma amino acids level was also studied. At the onset of the organ failure(s), the OG was 2.1 ± 1.9 ($mOsm/kg \cdot H_2O$) (M ± SD) in the patients with single organ failure, and 25.8 ± 15.8 in the patients with the MOF ($p < 0.001$). The OG was -3.7 ± 3.4 in survivors at the discharge from the ICU and the OG was 31.2 ± 22.7 in non-survivors immediately prior to their death ($p < 0.001$). These results indicate that the OG increased when the number of the failed organs or the number of the injured cells was increased. The calculation of non-amino acid OG revealed that even though approximately half of the increase in the OG was attributed to the increased amino acids level, the another half could express the blood level of unmeasurable solutes. These results suggest that the OG is a simply determinable and reliable index of the severity of the MOF patients and that the OG could be a good cellular injury score expressing the abnormal escape of the intracellular solutes caused by the impaired intracellular metabolism and the cell membrane malfunciton of the injured cells.

97 SALUTARY EFFECTS OF DOPAMINE AND CORTICOSTEROIDS ON SURVIVAL IN EXPERIMENTAL NEONATAL SEPTIC SHOCK. D. Gore*, T E. Lobe, C. Mantor*, R. Paone*, M. P. Griffin*, J. G. Hilton*, P. Mancillas*, D. L. Traber, D. N. Herndon. The Shriners Burns Institute, Galveston, TX 77550.

Often, neonates succumb to septic shock despite aggressive intervention. To assess the efficacy of high-dose dopamine and steroids in resuscitation, four randomly assigned groups of neonatal pigs were subjected to fecal-E.coli peritonitis-induced septic shock by intraperitoneal inoculation. Group I received no pharmacologic resuscitation, while Groups II-IV were resuscitated beginning when shock was apparent: Group II received methylprednisolone (30 mg/kg, IV) every 6 hours; Group III received dopamine hydrochloride (50 ug/kg/min); and Group IV received the combination of the two drugs. Hemodynamics and regional blood flow, assessed using radiolabeled microspheres, were not significantly different by ANOVA. Pigs "survived" if hemodynamics were stable at 24 hours when compared to baseline. Survival data are shown below:

	Group	(n)	Mean Survival In Hours (±SEM)	% Survivors
I	Controls	13	7.0 (0.8)	0
II	Steroids	8	18.9 (2.4)*	38%
III	Dopamine	5	17.8 (2.0)*	40%
IV	Combination	5	21.5 (1.2)*	40%

*$p<0.0005$ compared with Group I (Student's "t" test)

Steroids and dopamine each exert a beneficial influence on survival in this model, while their combination is no better than either of the drugs alone.

98 HOW DOES ARTERIAL BLOOD LACTATE RELATE TO OXYGEN DELIVERY AND HEMODYNAMIC VARIABLES IN NON-SEPTIC (NSS) AND SEPTIC SHOCK (SS)?
Johan Groeneveld*, Lambertus Thijs. Medical Intensive Care Unit, Dep. of Internal Medicine, Free University Hospital, 1081 HV Amsterdam, The Netherlands.

A retrospective study of 50 patients with circulatory shock was undertaken. From the records, first measured cardiac index (CI) (t=1) and highest CI (t=2) with concomitant hemodynamic and metabolic variables in arterial blood were taken. Nineteen patients had NSS and 31 SS, as defined by usual criteria. Mortality was equivalent. At t=1 and t=2, CI and oxygen delivery ($\dot{D}O_2$) were higher ($p < 0.001$) and systemic vascular resistance index (SVRI) was lower ($p < 0.001$) in SS than in NSS. With similar initial ABL values (median 4.8 in NSS vs 3.3 mmol/L in SS, n.s.) and increases in $\dot{D}O_2$ (median 30% in NSS vs 17% in SS, n.s.), arterial blood lactate (ABL) had fallen median 50% in NSS ($p < 0.01$) but had not changed in SS ($p < 0.0001$ NSS vs SS). Changes in ABL did not linearly correlate with changes in CI, $\dot{D}O_2$, mean arterial blood pressure, arterial pO_2, pH and time interval t=1 to t=2. In NSS, changes in ABL only correlated with changes in arterial oxygen content (CaO_2, $r = -0.65$, $p < 0.01$). In SS, changes in ABL best correlated with changes in SVRI ($r = -0.54$, $p < 0.01$). Anaerobic metabolism thus decreases in response to an increase in CaO_2, CI and thus $\dot{D}O_2$ in NSS but not in SS. ABL in the latter may relate to peripheral vasodilation, associated with peripheral shunting of blood transported oxygen, rather than to insufficient $\dot{D}O_2$.

99 ENDOTOXIN SHOCK AFTER RESUSCITATION FROM HEMORRHAGIC HYPOTENSION. Jureta W. Horton. Univ. of Texas Health Science Center, Southwestern Medical School, Dallas, Texas.

While adequate volume resuscitation has decreased mortality from hemorrhagic shock(HS), recovery in many patients is complicated by sepsis. To determine whether the subject debilitated by HS would exhibit greater cardiocirculatory dysfunction when challenged with sepsis, 10 dogs (Group I) were hemorrhaged to a mean arterial pressure(MAP) of 30mmHg. After 2 hr hypotension, shed blood and lactated Ringer's solution, 50 ml/kg, were given and the dogs were observed for 5-7 days. Ten dogs were sham-hemorrhaged and served as controls (Group II). On the experimental day, dogs were given endotoxin, 1 mg/kg IV. Endotoxin shock caused significant hypotension and acidosis and impaired regional perfusion in all dogs. Cardiac output (CO), stroke volume(SV), dP/dt, and left ventricular end-diastolic pressure(LVEDP)

fell to a similar extent in all dogs, regardless of a previous HS episode. Our data suggest that a previous HS insult, if adequately resuscitated, does not exacerbate cardiocirculatory dysfunction induced by endotoxin shock. (*Indicates $p<0.05$)

	CONTROL		60 MIN ENDOTOXIN		360 MIN POST ENDOTOXIN	
Groups	I	II	I	II	I	II
MAP, mmHg	110±6	127±7	51±4	44±6	82±10	77±9
CO, ml/min/kg	150±20	130±7	90±13	80±9.3	110±10	70±6.1*
SV, ml/beat/kg	1.6±0.2	1.43±0.10	1.1±0.2	0.74±0.10	1.3±0.2	0.71±.07*
LVEDP, mmHg	7.4±0.7	5.6±0.5	3.2±0.8	2.5±0.6	3.7±1.0	4.8±0.7
dP/dt, mmHg/sec	2625±150	2700±200	1900±143	1905±250	2000±250	2200±250
pH	7.33±.01	7.33±.01	7.28±.01	7.25±.02	7.24±.05	7.21±.04

100 INHIBITION OF LYMPHATIC PUMPING IN ENDOTOXIN SHOCK. M.Johnston.* R.Elias.* A. Hayashi* and W. Nelson.(Sponsor:W.Nelson) Departments of Pathology and Surgery, Sunnybrook Regional Trauma Unit, University of Toronto, Toronto, Ontario, Canada. M5S 1A8.

Lymphatic vessels control the removal of extravascular fluid and protein through their ability to contract and propel fluid. In order to study the effects of endotoxin on lymphatic pumping activity, a model system has been developed in sheep that permits the quantitation of lymphatic pumping in vivo without the complication of variable lymph inputs. A segment of intestinal lymphatic was isolated from all lymph input and provided with fluid from a reservoir. While the intravenous administration of E.coli endotoxin (3.3-33 ug/kg)resulted in 2 to 7 fold increases in lymph formation in conscious and anesthetized sheep, the endotoxin was found to suppress contractile activity and fluid propulsion in both groups. In addition to this systemic effect, intestinal lymph collected from animals that had received intravenous endotoxin, contained a host-derived factor(s) that inhibited lymphatic pumping when delivered to the vessel from the reservoir. This data suggests that a major contributing factor in the accumulation of extravascular fluid and protein in sepsis, is the combination of enhanced transvascular flux of fluid and protein with impaired lymphatic contractile activity and reduced interstitial drainage.

101 ENDOTOXIN IN SEVERE PERITONITIS ELIMINATED BY LAVAGE. H.O. Kleine* and H.G. Beger. Dept. of General Surgery, Univ. Ulm, Steinhoevelstrasse 9, 7900 Ulm, FRG.

19 patients were treated with definite surgery, triple antibiosis, and lavage intra- as well as postoperatively. The abdomen was primarily closed. Endotoxin (ET) daily measured by chromogenic limulus test decreased in the peritoneal fluid (EU range/ml) and in arterial or venous blood (EU max/ml) from the time of operation up to the 5th day (cf. table):

		Intraoperative measurements				Postop. (5th day)	
perforated organ	n	perit.fluid	blood	lav.fluid	blood	lav.fluid	blood
gastr.duod.ulcer	5	10^1 - 10^3	8(53)	10^1	10(24)	10^0	7(8)
gall bladder	2	10^2 - 10^3	20	0	14	10^1	2
small bowel	5	10^1 - 10^4	24(37)	0	5(24)	10^1	7(11)
colon	5	10^3 - 10^4	17(112)	10^0	19(146)	10^1	10(97)
appendix	2	10^3 - 10^4	-	0	-	0	-

5/19 patients needed reoperation. 3/19 died from persistent bacterial (EU max/ml), 1/19 from alcaline peritonitis, 1/19 from pulmonary insufficiency without peritonitis. Conclusions: The ET concentration in peritoneal fluid correlates with the perforated organ. The peritoneal layer effectively prevents ET invasion into the circulatory system. ET is almost eliminated by intraoperative lavage. Postoperative lavage keeps peritoneal ET low except for 16% of the patients with persistent bacterial peritonitis. This combined therapy was successfully applied in 86% of the the patients. The abdomen was primarily closed and only patients with persistent peritonitis were reoperated.

102 TOXIC EFFECTS OF BILIRUBIN ON CULTURED RAT HEPATOCYTES. K. Koizumi*, T. Sato, T. Nishihira*, I.K. Berezesky* and B.F. Trump. Univ. of Maryland, Dept. of Pathology and MIEMSS, Baltimore, MD 21201.

It is well recognized that sepsis is frequently accompanied by jaundice. In order to better understand the effect of jaundice on liver, we investigated the

changes in energy metabolism of cultured hepatocytes after exposure to bilirubin (Bil). Hepatocytes were isolated by in situ collagenase digestion, cultured in MEM containing supplements, and then exposed to 25, 50 and 100 μM Bil. Ketone body ratio (KBR: AcAc/β-HOB), which links mitochondrial redox, decreased significantly after exposure for 3 and 6 hrs, and recovered after 24 hrs. ATP decreased and lactate increased after 6 and 24 hrs. Total ketone bodies increased after 24 hrs. These data indicate that bilirubin has inhibitory effects on the respiratory chain at early stages (3, 6 hrs), and that despite recovery of the respiratory chain after 24 hrs, the ATP decreased, presumably due to the uncoupling effect of bilirubin. Fatty acid oxidation occurred to compensate for the decrease in ATP after 24 hrs, inducing an increase in total ketone bodies. Therefore, it is concluded that jaundice may possibly accelerate liver injury during sepsis. (NIH GM 32084.)

Bil (uM)	KBR			ATP (nmoles/mg)		*: P<0.05
	3 h	6 h	24 h	3 h	6 h	24 h
Cont	2.6±0.2	2.1±0.1	2.3±0.2	10.8±0.2	10.4±0.3	10.2±0.4
25	1.7±0.3*	1.6±0.2*	2.1±0.3	10.3±0.4	9.2±0.3*	7.4±0.6*
50	1.8±0.2*	1.4±0.2*	1.8±0.3	10.7±0.3	10.2±0.4	8.5±0.5*
100	1.0±0.1*	1.5±0.1*	1.9±0.2	11.3±0.4	9.3±0.5*	7.5±0.6*

103 EFFECTS OF INSULIN AND ENDOTOXIN ON SKELETAL MUSCLE AMINO ACID UPTAKE IN RENAL FAILURE. G. Kozeny* and M.M. Sayeed. Depts. of Medicine and Physiology. Loyola University Stritch Sch. of Med., Maywood, IL 60153.

This study evaluated the in vivo effects of endotoxemia on insulin dependent transmembrane amino acid (AA) uptake in renal failure (CRF). Male Holtzman rats (8/group) were sham operated (C) (BUN 19 ± 3, creat 0.4 ± .1) or had 7/8 nephrectomy (N) (BUN 160 ± 14, creat 1.9 ± .3) and pair fed for 12 days. Nineteen hours after i.v. injection of AA analog ^{14}C-α-aminoisobutyric acid (AIB), the rats were injected i.v. with Salomonella enteritidis endotoxin (E) (5 mg/kg, LD_{30}) or saline (S) followed in 3 hrs by i.v. insulin (0, .25, 1.0, 2.5 U/kg). Two hours later the rats were sacrificed and in vivo soleus muscle AIB content and extracellular inulin space determined. This allowed calculation of AIB intracellular to extracellular distribution ratio (DR) shown below as mean ± SE.

Insulin (U/kg)	C & S	C & E	N & S	N & E
0.00	9.2 ± .6 *	5.3 ± .3 *	5.8 ± .8 *	4.1 ± .4
0.25	10.9 ± 1.5 *	7.9 ± .8	7.9 ± 1.0	8.1 ± .8
1.00	15.4 ± .9	13.2 ± .5	11.4 ± 1.8	10.8 ± 1.9
2.50	16.2 ± .8	13.8 ± .6	9.3 ± .6	8.7 ± .6

These results demonstrate 1) CRF lowers basal AA flux, 2) CRF impairs insulin's ability to increase AA flux but not insulin's hypoglycemic action, 3) endotoxemia enhances the depressive effect of CRF on basal AA flux. * = $p < 0.05$.
(Support: NIH Grants GM32288 & HL31163).

104 HYPERTRIGLYCERIDEMIA OF GRAM-NEGATIVE SEPSIS IN THE RAT: ALTERED VLDL KINETICS AND IN VIVO HEPATIC LIPID SYNTHESIS. S. Lanza-Jacoby and A. Tabares. Department of Surgery, Jefferson Medical College, Philadelphia, PA

The mechanism for the development of hypertriglyceridemia during gram-negative sepsis was studied in 275-300 g rats after injection of $8x10^7$ live E. coli colonies per 100g body weight or physiological saline. For the first experiment all rats were fasted after injection to equalize the nutritional state. Twenty-four hours following E. coli injection serum triglycerides (trig), free fatty acids (FFA), and cholesterol (chol) of septic (S) rats were elevated by 179%, 51%, and 29% respectively, compared with the levels of control (C) rats. Serum insulin and glucagon levels of S rats were higher than C rats by 53% and 86%, respectively. The elevation of serum trig in S rats may be attributed to a decrease in the removal rate of VLDL, labeled endogenously with [2-^{3}H] glycerol. The rate of in vivo synthesis of trig, as measured from ^3H_2O, was higher in the livers of the S rats than in those of the C rats. The decreased rate of trig secretion and the increase in liver trig synthesis contributed to the 35% elevation of liver lipids in the S rats compared to their C. In a second series of experiments C and S rats were fed intragastrically a balanced solution containing glucose plus fat as the sources of nonprotein calories. Serum trig of the fed S rats were 25% less than the fed C rats while serum FFA and chol remained elevated during sepsis. In vivo synthesis of liver trig from [^{3}H] water was elevated by more than 2 fold in fed S rats compared with their fed C. There were no significant differences in skeletal muscle or heart lipoprotein lipase activity between both groups. The data imply that S rats in the fed state may have an increased ability to clear trig even when lipid synthesis is increased.

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105 DIETARY INDUCED DISTURBED BALANCE BETWEEN W6 AND W3 POLYUNSATURATED FATTY ACIDS (PUFA) IN LIVER LIPIDS IS ACCOMPANIED BY REDUCED SURVIVAL IN PERITONITIS. C. Larsson-Backström, E. Arrhenius*, K. Sagge*, J. Paprocki*, L. Lindmark*, L. Svensson*. KabiVitrum AB, S-112 87 Stockholm, Sweden.

PUFA and their metabolites have been suggested a role in septic shock. Changes in composition of PUFA in liver and survival during peritonitis was presently studied on rats (90 g) fed four diets (14% fat) for three weeks: low α-linolenic acid (ALA, ~7%), high ALA (~20%), low ALA + γ-linolenic acid (GLA, ~3%) and high GLA (~20%). Peritonitis was induced by i.p. E.coli (~LD_{50} dose). Liver samples were taken from fed (FE), fasted (FA) and septic-fasted (SF; survivors) rats at 24 hrs and analyzed for fatty acid profile in neutral lipids (NL) and phospholipids (PL). Results, in % of total fatty acids (X±SEM), on changes in arachidonic (20:4w6) and docosahexaenoic (22:6w3) acids (sign diff:°FA↔FE; *SF↔FA; #SF (low ALA)↔SF):

	low ALA;FE	low ALA;FA	low ALA;SF	high ALA;SF	low (ALA+GLA);SF	high GLA;SF
20:4w6,NL	3.47±0.10	14.51±1.22°	10.84±0.83*	3.87±0.63*#	5.45±0.61*#	14.01±2.80
PL	24.88±0.34	24.46±0.56	21.03±0.31*	25.58±0.20#	26.93±0.57#	29.60±0.50#
22:6w3 NL	1.10±0.08	3.10±0.15°	2.38±0.07*	2.14±0.28	3.13±0.47	0.82±0.12#
PL	7.03±0.19	10.30±0.66°	7.48±0.45*	8.24±0.23	7.82±0.09*	5.53±0.15#
Survival			50±9%	32±9%	38±8%	10±0%#

Most other PUFA:s were changed in opposite directions or remained unchanged. Conclusions: 1) Low dietary GLA increases 20:4w6 in PL almost as much as high GLA and relieve sepsis induced reduction of 20:4w6. 2) Survival from peritonitis is diminished by concomitant increase in 20:4w6 and decrease in 22:6w3 in liver.

106 VASCULAR CALCIUM METABOLISM AND PROTEIN PHOSPHORYLATION IN RAT INTRAPERITONEAL SEPSIS. Ray Z. Litten*, Joe A. Carcillo*, and Bryan L. Roth, Armed Forces Radiobiological Research Institute, Children's Hospital National Medical Center and George Washington University Medical School, and Surgical Research Branch, Naval Medical Research Institute Bethesda, MD 20814-5055.

Alterations in vascular contractility have been well documented in sepsis and septic shock, and may involve either extrinsic factors (prostaglandins, enkephalins, etc.) or may be intrinsic to vascular smooth muscle. McKenna et al (Circ Shock, 1986) previously demonstrated alterations in aortic contractility in rat intraperitoneal sepsis. We here demonstrate alterations in receptor-mediated protein phosphorylation and calcium metabolism in rat intraperitoneal sepsis. Using [32P]-orthophosphate-labelled rat aortic rings we found substantial decrements in the alphal-adrenergic mediated phosphorylation of myosin light chain--a major contractile protein in vascular tissue ($p < 0.05$ vs sham operated animals). Phosphorylation was quantified after sodium dodecylsulfate-polyacrylamide gel electrophoresis and autoradiography by a scanning laser densitometer. Calcium flux through voltage gated calcium channels was determined using 45Ca++. Significant alterations in calcium influx were noted after 5 min of alphal-adrenergic receptor stimulation ($p < 0.05$ vs sham). These results demonstrate signficant alterations in aortic protein phosphorylation and calcium metabolism in rat intraperitoneal sepsis. Supported in part by MR 04120.05.

107 CHANGES IN THE DISTRIBUTION OF MAJOR CLASSES OF PHOSPHOLIPIDS AND IN THE FATTY ACID COMPOSITION OF PHOSPHOLIPIDS IN CARDIAC SARCOLEMMA FOLLOWING ENDOTOXIN DMINISTRATION Maw-Shung Liu and Ge-Fei Kang. St. Louis Univ. Sch. Med., St. Louis, M. 63104

The major classes of phospholipids and the fatty acid (FA) composition of phospholipids in cardiac sarcolemma prepared from control and endotoxin-injected dogs were analyzed. The results show that 4 hr following endotoxin administration (0.5 mg/kg;iv), phosphatidylcholine (PC) and phosphatidylethanolamine (PE) contents were decreased by 8.3% ($p<0.05$) and 14.6% ($p<0.05$), respectively, while lysophosphatidylcholine (LPC) and lysophosphatidylethanolamine (LPE) were increased by 283% ($p<0.05$) and 131% ($p<0.05$), respectively. Cardiolipin was decreased by 38% ($p<0.05$) while phosphatidylinositol, phosphatidylserine, and sphingomyelin contents were not significantly affected 4 hr post endotoxin. Analyses of the FA composition reveal that not only the unsaturated FA (18:1) was decreased in PC while both saturated and unsaturated FAs (18:0 and 20:4) were decreased in PE. Analyses of lysophosphatides show that both saturated and unsaturated FAs were increased in LPC and LPE. Examination of free FAs indicate that FAs with a chain length greater than 16C (C16 to C22), both saturated and unsaturated, were increased by endotoxin

administration. These data demonstrate that the molecular structure of cardiac sarcolemmal lipids was greatly modified by endotoxin administration. A modification of membrane lipid structure would alter the physical properties of membrane lipids and the dynamics of membrane-associated enzyme and receptor systems, and ultimately affect metabolism and function of the myocardial cell. (Supported by NIH grants HL-33008 and GM-31664).

108 THE INFLUENCE OF ANESTHESIA AND HYPERTENSION ON SKELETAL MUSCLE MICROCIRCULATORY RESPONSES TO HYPERDYNAMIC E. COLI SEPSIS. A.S. Luebbe*, P.D. Harris, H.M. Cryer*, and R.N. Garrison. Depts Physiology and Surgery, Univ of Louisville, Kentucky 40292

To determine if hypertension or pentobarbital anesthesia alters microvascular reactivity during hyperdynamic sepsis, we infused (i.v.) live E.coli ($6x10^8$CFU/100g) into normotensive and renovascular-hypertensive (1K-1C) rats (160-175 g). Cardiac output (Q), blood pressure (BP), and diameters of large (A1) and small (A3/A4) cremasteric arterioles were measured as a percent of baseline (BL) in decerebrate (DEC) and pentobarbital(PB)-anesthetized (50 mg/kg) rats (* is HT-PB vs NT-PB):

	normotensive-DEC (n=5)		normotensive-PB (n=8)		hypertensive-PB (n=6)	
	BL	30 min	BL	30 min	BL	30 min
BP	106±3 mmHg	98±2%	124±3 mmHg	94±2%	*160±8 mmHg	102±2%
Q	82±6 ml/min	120±3%	95±7 ml/min	106±4%	89±7 ml/min	122±6%
A1	115±3 µm	90±3%	86±3 µm	90±2%	*66±5 µm	100±5%
A3	34±4 µm	109±3%	14±1 µm	132±12%	20±4 µm	*96±9%
A4	16±1 µm	142±9%	7±1 µm	135±10%	7±1 µm	*105±9%

In normotensives, pentobarbital anesthesia blunted the increase in cardiac output; however, large A1 constricted and small A4 dilated during sepsis in both anesthetized and decerebrate rats. In pentobarbital-anesthetized hypertensives, large A1 did not constrict, and small A4 did not dilate during sepsis. Yet, the small A4 had vascular tone since nitroprusside (10^{-5}M) dilated them to 187±12% in normotensives and to 177±10% in hypertensives. Thus, microvascular mechanisms specific to sepsis have been blunted in the hypertensive rat. (VAMC; AI 22098)

109 THE EFFECT OF ALPHA-ADRENERGIC BLOCKADE ON CELLULAR Ca^{2+} MOBILIZATION IN HEPATOCYTES DURING ENDOTOXIC SHOCK. S.R. Maitra*, J.A. Guszcza*, and M.M. Sayeed. Dept. of Physiol., Loyola University Stritch Sch. of Med., Maywood, IL 60153.

Effect of α-adrenergic receptor antagonists phentolamine (Phentl) and prazosin (Praz) on cytosolic Ca^{2+} concentration $[Ca^{2+}]_c$ was studied in hepatocytes during endotoxic shock. Rats were given iv injections of endotoxin (20 mg/kg) (ETX), Phentl (3 mg/kg) + ETX (20 mg/kg), or Praz (5 mg/kg) + ETX (20 mg/kg). They were killed 5 hrs later at which time endotoxin rats showed signs of shock. Isolated hepatocytes were prepared and employed for the measurements of $[Ca^{2+}]_c$ under basal and hormone stimulated (1 and 10 µM epinephrine) conditions by means of the Quin 2 fluorescence technique. The apparent basal level of $[Ca^{2+}]_c$ in ETX rat hepatocytes (mean ± SE = 482 ± 31 nM) was significantly higher ($p<.05$) than in Phentl + ETX (242 ± 73) and Praz ± ETX (240 ± 43) groups. A significant increase in $[Ca^{2+}]_c$ occurred after stimulation with epinephrine in Phentl + ETX and Praz + ETX, but not in ETX rat hepatocytes. ETX rats showed a mortality rate of 82% which was significantly attenuated in α-adrenergic receptor antagonist treated groups. These data suggest that the protective effect of α-adrenergic receptor antagonists during endotoxic shock may be mediated, in part, by attenuating the entrance of Ca^{2+} into endotoxic liver cells. (Support: NIH Grants GM32288 and HL 31163).

110 ECMO THERAPY FOR INFANTS WITH BETA STREPTOCOCCAL SEPSIS, M. Miller, B. Short, George Washington University School of Medicine, Children's Hospital National Medical Center, Washington D.C. 20010

Neonates with fulminant bacterial infections can die in septic shock despite our aggressive medical therapy. From 6/84 to 11/86, 10 infants with septic shock were treated at CHNMC with veno-arterial extracorporeal membrane oxygenation(ECMO). All

infants had failed conventional therapy and met criteria predicting an 80% mortality. Diagnosis was by positive blood culture in 7, by positive Wellcogens for GBS antigen in 1, and by compatible perinatal hx. in 2. Eight infants had total WBC's 6600 prior to ECMO. All ten infants survived with ECMO therapy. Morbidity among these infants included: (1) Intracranial hemorrhage in 4;(2) oxygen dependence beyond one month in 3 infants. The risk of ICH was higher in the septic shock infants than in our ECMO population in general (40 vs 26%). Likewise, the risk for chronic lung disease was higher in the septic shock infants than our ECMO population (30 vs 15%). In our experience ECMO significantly improved survival (from a predicted 20% to 100%) and is therefore a valid therapy for septic term infants unresponsive to present therapies. The morbidities are higher in this population, but should not preclude their treatment with ECMO.

111 POTENTIATION OF MORTALITY BY E. COLI STRAINS AND B. FRAGILIS INTERACTIONS IN A RAT INTRA-ABDOMINAL ABSCESS MODEL. J. Glenn Morris*, Ben D. Tall*, Linda D. Lapierre*, John H. Siegel, Thomas C. Vary. Cent. Vac. Dev. and MIEMSS:Depts. of Surgery, Physiology, UMAB, Baltimore, MD 21201.

A rat intra-abdominal abscess model was used to investigate differences in mortality (48 hours post inoculation) produced by 3 strains of Escherichia coli (EC) given together with Bacteroides fragilis (BF). Intra-abdominal abscesses were created by the intraperitoneal introduction of a fecal-agar pellet (1.5 ml vol.) containing known concentrations of EC (3 strains EC1, EC2,EC3) and BF. Abscess formation was observed in all animals. No early mortality (48h) was seen with sterile and BF (in concentrations up to 10^9cfu) monoclonal pellets. Mortality at 48h was seen with EC1 alone, although the LD_{50} was > 10^6cfu. With an inoculum containing both EC1 and BF, mortality was increased over the respective monoclonal abscesses with an LD_{50} of $4X10^2$cfu EC1, when combined with 10^8cfu BF. The mortality with the biclonal pellet was modulated by changing the E.C. strain present. With an inoculum containing both EC2 and BF, mortality was increased (LD_{50} reduced to < 10^1cfu EC2 when combined with 10^8cfu BF). In contrast, an inoculum containing up to $1X10^8$cfu EC3 and $1X10^8$cfu BF, no early mortality was observed. Our data suggest that in low virulence E. coli, early mortality is potentiated by E. coli dependent factors when B. fragilis are also present in an abscess. These data also indicate that there are clear differences in virulence between E. coli strains, with only certain strains able to cause early mortality after intra-abdominal inoculation.

112 EFFECT OF HYPERBARIC OXYGENATION IN A RAT MODEL OF INTRA-ABDOMINAL SEPSIS. K.H. Muhvich*, R.A.M. Myers and L. Marzella Department of Pathology, School of Medicine and Division of Hyperbaric Medicine, Maryland Institute for Emergency Medical Services Systems, University of Maryland, 10 S. Pine Street, Baltimore, Maryland, 21201, U.S.A.

A deficit of oxygen utilization in tissues is a hallmark of uncontrolled sepsis. Trauma, hypoperfusion and inflammation also create areas with low oxygen tensions in tissues. These hypoxic regions favor the growth of strict anaerobic bacteria. Anaerobes in turn promote the establishment of aerobes. Changes in oxygen tension may thus modify metabolic and bacterial factors and influence the severity of sepsis. We have characterized the effects of hyperbaric oxygenation alone or in combination with surgical intervention and/or antimicrobial agents in a rat model of intra-abdominal sepsis. To this end Bacteroides fragilis and/or Escherichia coli were inoculated into the peritoneal cavity of 200 rats. Mortality, bacterial numbers and host responses were evaluated 72 hours after rats received the bacterial inoculum. Hyperoxia did not alter mortality or other host factors when used as an adjunctive treatment. However, hyperoxia used alone increased mortality if E. coli was present in the inoculum. In conclusion, the addition of hyperbaric oxygen to appropriate therapy for intra-abdominal sepsis did not compromise the host factors measured and to a small extent decreased bacterial numbers.

113 CORONARY CONTRACTION-RELAXATION RESPONSES IN CANINE ENDOTOXIN SHOCK. J.L. Parker, R.S. Keller*, D.V. DeFily*, M.J. Novotny*, H.R. Adams. Dalton Research Center and Dept. Veterinary Biomedical Sciences, University of Missouri, Columbia, MO 65211.

Contractile function of coronary vascular smooth muscle in canine endotoxin shock (ES) was evaluated *in vitro* using left circumflex coronary ring preparations. Large (1.5-2.0 mm OD) and small (0.5-1.0 mm OD) vessels were isolated from animals 4 hrs after IV administration of either saline (control; C) or 1.5 mg/kg purified *E. coli* endotoxin (ES); ES dogs exhibited marked hypotension and cardiovascular depression. Coronary vessels were individually stretched to the apex of the length-contraction relationship prior to evaluation of contractile responses. Isometric contractions obtained in response to increasing concentrations of KCl (5-100 mM) and $PGF_{2\alpha}$ (10^{-10}-$3x10^{-5}$M) were similar in both C and ES coronary vessels; maximal contractile tension and ED_{50} values were not significantly different for both large and small vessels. *Inhibitory responses to nitroprusside (NP; 10^{-10}-10^{-4}M), a cGMP-dependent vasodilator,* were similar in C and ES vessels, and NP inhibited $PGF_{2\alpha}$ contractions more effectively than KCL contractions. For example, NP IC_{50} values for C and ES large coronaries averaged 44±9 vs 42±11 nM (P>0.05) in vessels precontracted with $PGF_{2\alpha}$, and 570±140 vs 714±312 nM (P>0.05) in vessels precontracted with KCL. Results were similar in C and ES coronary vessels with endothelium removed. We conclude that both depolarization (KCL) and receptor ($PGF_{2\alpha}$)-mediated contractile mechanisms, as well as cyclic GMP (NP)-mediated vasodilation mechanisms, remain functional in coronary vasculature isolated from this shock model. (Supported by NIH RCDA HL-01669 and American Heart Assoc.)

114 PLASMA CONCENTRATIONS OF ENDOTOXIN (LPS) FOLLOWING JUGULAR OR PORTAL INJECTIONS OF LPS, GI STRANGULATING-OBSTRUCTIONS AND AFTER COLON RUPTURE. G Bottoms, J Fessler, S Gimarc*, G Coppoc*, Purdue University, West Lafayette, IN 47907.

Endotoxin was quantitated in equine plasma using Travenol LAL Chromogenic Testing Procedure. The assay was validated for the smallest amount of LPS that could be added to plasma and measured reliably (30 pg/ml), intraassay precision (CV=5.5%), interassay precision (CV=11%), recovery (93%) and stability of frozen samples (at least 90 days). Baseline plasma concentrations of chromogen activating material (CAM) was 23 ± 21 pg/ml. Plasma concentrations following a jugular injection of LPS (3ug/kg) revealed a concentration of 4532 ± 812 pg/ml in the 2 minute sample after injection. Preliminary pharmacokinetic analysis indicate that the initial T 1/2 was < 2 min. The kinetics are complex and there is a prolonged plateau of LPS or CAM at levels just above baseline. When LPS (3 ug/kg) was injected into the portal vein, the systemic plasma concentration of CAM in the 2 minute sample was only 711 pg/ml. The concentrations of CAM in plasma collected from horses with experimentally induced strangulating-obstructions were not increased above baseline. The concentration in plasma from one horse with a ruptured ventral colon was increased (128 pg/ml). Samples collected from 10 horses suffering gastrointestinal obstructions revealed values ranging from baseline to 89 pg/ml. The results indicate that LPS is rapidly cleared from the circulating blood and that only in very severe GI problems does it increase above baseline. Whether the pathophysiological changes following GI obstruction problems are caused by these very low concentrations of LPS or by other plasma mediators remains to be determined. (Supported by USDA and AQHA).

115 RIGHT VENTRICULAR DYSFUNCTION IN PATIENTS WITH SEPTIC SHOCK. J.F. Dhainaut, J.J. Lanore, J.M. de Gournay, M.F. Huyghebaert, F. Brunet, D. Villemant, A. Carli and J.F. Monsallier. Medical ICU, Cochin Univ. Hospital, F 75674 Paris Cédex 14.

An important factor contributing to the high mortality in septic shock is probably right ventricular (RV) dysfunction (Kimchi et al JACC 4 : 945, 1984). To analyse the RV performance during the first 2 days of septic shock, 23 such pts (mean age : 47 yrs) were studied. RV performance was evaluated by thermodilution technique using a pulmonary artery (PA) catheter with a rapid response thermistor and a REF 1 prototype (Edwards Lab.) calculating both cardiac output and RV ejection fraction (EF). This investigation was performed at the onset of septic shock (Do) after volume expansion and inotropic drugs as needed and 2 days later (D2). Results : 9 survived (S), 14 did not (NS).

	PAP		EF		EDP		EDV	
	Do	D2	Do	D2	Do	D2	Do	D2
S	23	20	.32	.31	7	8	137	141
NS	26	29*	.29	.22**	10	14**	155	154

EDV = end-diastolic volume (ml/m^2), P = pressure (mm Hg),*p<.01 Do vs D2,*S vs NS. Both S and NS showed a similar initial RVEF impairement (normal values : .45 ± .05). 2 days later in NS, EF fell despite a similar EDV, a slight increase in PAP (ns), and a higher level of inotropic drugs than in S, advocating for impaired contractility-induced a gradual fall in RV performance.

116 THE EFFECTS OF MONOKINES ON CALCIUM-SIGNAL TRANSDUCTION IN ISOLATED HEPATOCYTES AND NEUROBLASTOMA CELLS L. Kilpatrick-Smith, S. D. Douglas* and B. E. Corkey* Depts. of Pediatrics and Biochemistry, Univ. of Pennsylvania Med. Sch., Phila, PA 19104

The monokines, interleukin-1 (IL-1) and cachectin/tumor necrosis factor (TNF), may be responsible for the lethal effects of endotoxin. Many agonists mediate cellular events via fluctuations in cytosolic free calcium $[Ca^{2+}]_c$. The effects of purified human recombinant Il-1 and TNF on agonist induced increases in $[Ca^{2+}]$ were examined in isolated rat hepatocytes stimulated by vasopressin (VP) and in mouse neuroblastoma cells (NB) stimulated by bradykinin (BK) and nerve growth factor (NGF). $[Ca^{2+}]_c$ was measured fluorometrically in Fura-2 loaded cells. In hepatocytes, IL-1 (1.5 U/ml) produced a 2 fold rise in $[Ca^{2+}]_c$ (basal level=150 nM) which was dependent on extracellular Ca^{2+}. In contrast, TNF (1-100 U/ml) did not affect $[Ca^{2+}]_c$. VP (20 nM) induced elevation in $[Ca^{2+}]_c$ (3 fold) was inhibited by IL-1 but not by TNF. Thus, IL-1 which triggers a rise in $[Ca^{2+}]_c$ also inhibits the VP induced Ca^{2+} changes. In NB, TNF or IL-1 did not change $[Ca^{2+}]_c$ nor did they suppress the $[Ca^{2+}]_c$ response stimulated by BK (1 ug/ml). NGF (1 ug/ml) increased $[Ca^{2+}]_c$ by 4 fold (basal level=70 nM), an effect inhibited by TNF (100 U/ml) but not by IL-1. IL-1 alters $[Ca^{2+}]_c$ in hepatocytes but not in NB which suggests that IL-1 interacts with tissue specific receptors. While TNF does not alter $[Ca^{2+}]_c$, it does inhibit the Ca^{2+} response to NGF indicating a different mechanism. Septic shock affects Ca^{2+} homeostasis and diminishes responsiveness to agonists in various tissues. Thus, endotoxin-macrophage interaction may lead to monokine release which produces these alterations. (Supported by NIH PO1-NS-[illegible]52)

117 CARDIAC FUNCTION AND CORONARY FLOW IN LONG-TERM ENDOTOXEMIA. K. Lee*, S. Dziuban*, H. van der Zee* and R. Goldfarb, Albany Medical College, Albany, NY 12208.

We recently have reported that cardiac contractile function was depressed during long-term, low-dose endotoxemia. We found that cardiac function, as evaluated by the end systolic pressure diameter relationship (ESPDR) was depressed during endotoxemia while heart rates and systolic pressures were evaluated during what was previously termed "hyperdynamic" sepsis. Since the relationship between cardiac function and the adequacy of coronary flow is well known, we sought to determine if during this period of "hyperdynamic" sepsis coronary flow was compromised. Pigs were preinstrumented with coronary and pulmonary artery flow probes, left atrial catheter, left ventricular short axis ultrasonic crystals and pressure gauge. After one week's basal recordings, an endotoxin loaded osmotic pump was implanted, calculated to deliver 10 ug/kg/hr S. enteritidis i.v. Cardiac dynamic and flow recordings were obtained 10-15 times a day for the next 5 days or to expiration. As previously reported, ESPDR was depressed during endotoxemia becoming maximal on days 2 and 3. No significant changes were noted in coronary flow (ml/min) but the ratio of flow per beat to stroke work was depressed. Furthermore, the increase in coronary flow in response to an increase in work induced by increasing peripheral resistance was attenuated during endotoxemia. These findings suggest that the mechanisms controlling coronary flow are altered by long-term endotoxemia. (HL-35825)

118 RENAL PROTECTION OF DUAL CYCLOOXYGENASE AND LIPOXYGENASE BLOCKADE DURING ENDOTOXEMIA. John C. Passmore and Jamie S. Young*. Univ. of Louisville, Louisville, KY 40292.

Eicosanoids have been implicated in acute renal failure resulting from endotoxic shock. Blockade of leukotrienes or thromboxanes ameliorated the endotoxin induced fall in renal blood flow that was found in untreated rats (Badr et al, Kidney Internat. 30:474, 1986). The purpose of this study was to determine if dual blockade of both lipoxgenase and cyclooxygenase would provide more complete protection of renal hemodynamics and renal function during endotoxemia. Ibuprofen (cyclooxygenase blocker, Upjohn Corp.) and propyl gallate (lipoxygenase blocker) or LY171883 (leukotriene antagonist; Lilly Co.) were administered simultaneously. Cardiac output (CO), renal blood flow (RBF) and small intestinal blood flow (SIBF) were measured with radioactive microspheres: a) following dual blockade and b) 2 hours after endotoxin. Endotoxin alone (3 mg/kg iv, chloralose anesthesia) induced a 47% decrease in CO ($P=.05$), a 27% decrease in RBF ($P<.01$) and a 50% decrease ($P<.01$)in SIBF. Urine formation in endotoxin injected dogs was inadequate for clearance studies. Endotoxin injection into the dual blocked dogs induced no decline in CO or RBF. GFR was 23 ± 5 ml/min after dual blockade and 28 ± 5 ml/min after endotoxin. SIBF appeared to decline from .72 ± .25 to .25 ± .04 ml/min .g after endotoxin. Dual cyclooxygenase and lipoxygenase blockade appears to provide complete protection for renal hemodynamics during endotoxemia. Supported by American Heart/KY Affiliate.

119 DICHLOROACETATE REVERSES GLUCOSE DOWN-REGULATION AND INCREASED BCAA UTILIZATION AND DECREASES MUSCLE CATABOLISM IN SEPSIS. John H. Siegel, Thomas C. Vary, Robert Placko*, J. Glenn Morris*, Ben D. Tall*. MIEMSS and Departments of Physiology, Surgery and Geographic Medicine, University of MD, Baltimore, MD 21201.

Sepsis has been shown to decrease skeletal muscle glucose oxidation by inhibiting pyruvate dehydrogenase activity (PDHa) with increased proteolysis and use of BCAA. The effects of dichloroacetate (DCA) (1mmol/kg) which reversed PDH inhibition ($p<0.001$) were studied in skeletal muscle from a septic (S) rat model of intraabdominal abscess (E. coli + B. fragilis) and compared to control (C) and sterile abscess (SA). Septic (S), but not SA rats had an increase in muscle lactate concentrations over C, but no changes in pyruvate. After DCA, both lactate and pyruvate were reduced ($p<0.001$) to the same level in all S, SA, C. Muscle alanine concentrations which were increased in SA ($p<.05$) were reduced 3-fold in C, S and SA ($p<0.001$) after DCA suggesting that alanine synthesis may be limited or impaired due to decreased pyruvate availability. Muscle leucine (L) and isoleucine (I) levels were increased in sepsis, but after DCA L and I levels were reduced ($p<0.05$). Muscle phenylalanine concentrations were significantly elevated in sepsis compared to C or SA, and were reduced ($p<0.05$) after DCA in sepsis but not in C or SA animals. Depressed glutamine (G) levels in SA were also increased by DCA. Decreased muscle phenylalanine associated with lowered BCAA and increased glutamine suggests DCA may decrease septic muscle protein catabolism, and/or enhance protein synthesis. (Support by GM 36139 from NIGMS).

120 PROTEIN KINASE C ACTIVITY IN LIVER AND SPLEEN IN CONTINUOUS ENDOTOXEMIA. J.A.Spitzer and I.V. Deaciuc, Department of Physiology, Louisiana State University Medical Center, New Orleans, LA 70112

Previous work from this laboratory implicated activation of protein kinase C (PKC) as part of the mechanism of action of endotoxin (ET) (Spitzer, J.A. and E.R. deTurco, VIth International Conference on Cyclic Nucleotides, Calcium and Protein Phosphorylation, Signal Transduction in Biological Systems, Sept. 2-7, 1986, Bethesda, MD). Currently, we measured PKC activity in the cytosol (supernate of 105,000 g for 60 min) and membranous components (pellet of the above centrifugation) of hepatocytes and spleen lymphocytes of male, Sprague-Dawley rats that had been infused continuously with a non-lethal dose of ET or sterile saline (SAL) for 30 h (Fish, R.E. and J.A. Spitzer, Circ. Shock, 12, 135-149, 1984). At this time point we have previously demonstrated reduced α_1-adrenergic and vasopressin-related functional properties in hepatocytes, consistent with negative feedback regulation (Deaciuc, I.V. and J.A. Spitzer, Am. J. Physiol. 251, R984-R995, 1986). Cytosolic PKC of spleen lymphocytes of ET-infused rats was 231% of that of SAL-infused rats, 3265 vs 1414 $U.mg^{-1}$ pro-

tein. The same PKC activity of hepatocytes in 2 out of 3 experiments was 227% of their SAL-infused counterparts, 280 vs 123 $\mu U.mg^{-1}$ protein. Membrane-associated PKC activity was not significantly altered in either cell type. These results suggest that PKC-mediated effector mechanisms may contribute to the pathophysiologic consequences of continuous endotoxemia. (Supported by NIH grants GM 30312 and GM 32654).

121 COMPLEMENT ACTIVATION AND PROTEASE INHIBITORS IN HUMAN SEPTIC SHOCK
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In 23 patients with sepsis and septic shock serial (6 hourly) measurements were performed of C3a, functional C1-esterase inhibitor (C1-inh) and α2 macroglobulin (α2M), $\overline{C1}$-C1-inh complexes and proteolytically inactivated C1-inh (iC1-inh) using newly developed high sensitive assays. Ten patients survived.
Results: largely fluctuating levels were observed during the course of septic shock. C3a was uniformely markedly elevated, highest levels in nonsurvivors. Levels of functional inhibitors C1-inh and α2M were lowered. In some patients increased levels of $\overline{C1}$-C1-inh were present. Marked increased levels of iC1-inh were found in all patients.
Conclusions: these findings indicate activation of the complement system, most pronounced in nonsurvivors and proteolytic inactivation of C1-inh, suggesting loss of regulatory function of C1-inh as a possible pathogenetic mechanism in septic shock.

122 **A COMPARISON OF HYPEROSMOTIC AND HYPERONCOTIC RESUSCITATION FROM SEVERE HEMORRHAGIC SHOCK IN DOGS.** I.T. Velasco, Marly A. Oliveira*, Maria A. Oliveira* and M. Rocha e Silva. Instituto do Coração, Fac. Med. Univ. São Paulo, 05403, São Paulo, Brasil.

The effects of hyperosmotic NaCl (S, 7.5%), hyperoncotic dextran 70 (D, 6%) and their combination (SD) were compared for resuscitation of severe hemorrhage in 72 pentobarbital anesthetized (25 mg/kg) dogs. Two shock durations (45 or 75 min at 37 mmHg; blood loss: 51 ml/kg) and 2 doses (4 or 6 ml/kg) were employed. Survival (96 h), mean arterial pressure (MAP), cardiac index (CI), systemic vascular resistance (SVR), plasma volume (PV), sodium (Na) and osmolarity (OSM) were measured. Analysis of variance (contrasts for solutions (S vs D vs SD), shock durations (45 vs 75 min) and doses (4 vs 6 ml/kg) was employed. **RESULTS**: Survival rates: Solutions (n=24 for each): S: 58%; D: 46%; SD: 75%; Shock durations (n=36 for each): 45 min: 70%; 75 min: 50%; Doses (n=36 for each): 4 ml/kg: 47%; 6 ml/kg: 72%. MAP recovered to a stable 91 mmHg over 3 h, no differences between solutions, durations or doses. CI recovered to 88% of CTRL, 5 min after SD or S, but only to 39% of control after D. But at 3 h, CI was similar for S, D and SD, at 50% of CTRL. The larger dose produced a higher CI, but shock duration did not affect this parameter. PV, which was reduced to 52% of CTRL by shock, was increased by the three solutions (SD to 87%, S to 81%, D to 68% of CTRL), at 5 min, but at 3 h there were no differences between solutions (62% of CTRL). SVR was transiently decreased by S and SD (at 5 min), but not by D. Na and OSM were increased (to 150-155 mEq/l and 320-325 mOsm/l) by S and SD. **CONCLUSION**: the hyperosmotic-hyperoncotic combination, at the dose of 6 ml/kg is the most efficient resuscitative procedure.
(Research supported by FINEP, FAPESP and Fundação E.J. Zerbini.

123 IMPROVED RESUSCITATION OF HEMORRHAGIC SHOCK AFTER ADDING HIGH CONCENTRATIONS OF DEXTRAN 70 TO HYPERTONIC SALINE. JC Walsh*, PR Perron*, DC Lindsey*, JW Holcroft and GC Kramer, Depts. Human Physiol. and Surgery, Sch. Med., Univ. Calif., Davis, CA 95616.

Small volumes of hypertonic saline, 7.5% NaCl (HS), with 6% dextran 70 (Dx) added have been shown to more effectively resuscitate hemorrhaged sheep, pig and dog than HS alone. The present study compares resuscitation of hemorrhage using 1) HS-24% Dx, 2) HS-6% Dx and 3) HS alone. Conscious sheep were bled 37.5 ± 7.8 ml/kg to mean arterial pressure (MAP) of 50 mm Hg for 2 hrs. Resuscitation was performed with 100 ml of test solution. MAP rapidly increased from hemorrhage levels of 46-52 mm Hg towards baseline with all solutions. However, this effect was more sustained with

HS-24% Dx, less so with HS-6% Dx and least with HS alone. Average data are shown during baseline (BL), hemorrhage and specific times after resuscitation.

	Cardiac Output % baseline				Oncotic Pressure mm Hg			
	Hem	15 min	1 hr	3 hr	BL	Hem	15 min	3 hr
HS-24% Dx	38	95	103	100	21.4	14.2	15.2	13.6
HS- 6% Dx	40	73	79	85	21.5	12.6	12.1	12.1
HS alone	40	60	62	70	20.6	14.0	11.4	12.8

We used the fall in hemoglobin after infusion of each fluid to estimate plasma volume (PV) expansion. HS increased PV 16.6%, HS-6 increased PV 20.8% and HS-24 increased PV 45.0%. Infusion of 100 ml of HS-24% Dx after a blood loss of 1722 ml expanded plasma volume an estimated 635 ml and maintained cardiac output at 95% of baseline or better for 3 hours. CONCLUSIONS: The addition of a high concentration of dextran 70 significantly improves the effectiveness of resuscitation with small volumes of hypertonic saline. (DOD contract DAMD 17-86-C6115 and HL-18010)

124 SHOCK IN PATIENTS RECEIVING MASSIVE TRANSFUSIONS. R. Wilson, S. Dulchavsky*. Wayne State Univ., Detroit, MI 48201

Patients requiring massive transfusions have varying periods of shock, with multiple complications and a very high mortality rate. The case records of 397 patients receiving 401 transfusions of 10 or more units of blood within a 24 hour period from 1980 to 1986 were reviewed. The overall mortality rate was 47%. All 18 patients receiving 50 or more transfusions died. Of 175 patients having shock > 30 min, 116 (66%) died, of 226 having less shock, 80 (35%) died (Table). Platelet counts less than 50,000/mm^3, PT prolonged by five or more seconds and PTT prolonged to more than 50 sec. occurred in over 50% of patients studied. The average core temperature was 33.2 ± 1.6°C, and core temperatures less than 32.0° were over 85% fatal. Severe hypocalcemia (total Ca < 6.0 mg/dl and/or ion Ca^{++} < 0.75 mmol/L) occurred in > 50% of patients studied. Over 85% of survivors developed serious infections, especially gram negative pneumonias; 74% occurred within 48 hours and 18% occurred 30 or more days later from sepsis.

MORTALITY RATE

Shock > 30 min	Pre-exist Disease	Units of Blood 10 - 19	20 - 29	30 - 39	40 +
-	-	13/115 = 11%	11/32 = 34%	7/13 = 54%	6/9 = 67%
+	-	39/75 = 52%	14/21 = 67%	8/15 = 53%	20/25 = 80%
-	+	26/37 = 70%	11/13 = 85%	4/5 = 80%	2/2 = 100%
+	+	19/22 = 86%	8/9 = 89%	4/4 = 100%	4/4 = 100%
Total		97/249 = 39%	44/75 = 59%	23/37 = 62%	32/40 = 80%

125 **HYPERTONIC SODIUM CHLORIDE (7.5%) FOR THE INITIAL RESUSCITATION OF HYPOVOLEMIC PATIENTS.** R.N. Younes*, F. Aun*, D. Birolini*, N.T. Kawahara*, L. Casale*, C. Accioly*, I. Szajnbok*, N. Takeuti*, N.D. Mori* and P.L. Brito*. (Spon M. Rocha e Silva). Dept. Surgery, Fac. Med. Un. Sao Paulo, Sao Paulo, Brasil.

Thirty three patients admitted to the emergency ward in hypovolemic shock (mean arterial pressure < 60 mm Hg) were randomly assigned to Group I (18 patients) who received hypertonic NaCl (7.5% - HS) through a peripheral vein, or group II (15 patients) who received isotonic NaCl (IS), both at an infusion rate of 10 ml/min over 15 min. No other fluid was given after the infusion unless MAP fell below 80 mm Hg, or untill typed/cross-matched blood became available for preoperatory replacement. Patients were excluded from the study as soon as given fluid or blood. MAP was measured every 2 min, osmolarity, Na, Ht and plasma proteins before and after the infusion (Table I). A steady MAP increase occurred in 15/18 HS patients, reaching 80 mmHg during the infusion, while no IS patient ever reached this pressure, all being excluded at the end of the infusion. MAP was significantly different ($p < 0.001$) between groups during and after infusion. CONCLUSIONS: HS was effective as initial resuscitative procedure for human hypovolemia. The peripheral vein used for HS showed no inflammatory alterations during their evolution.

TIME (min)	MAP (mmHg) HS	IS	OSM (mOsm/l) HS	IS	Na (mEq/l) HS	IS	Ht (%) HS	IS	Pl Prot (g/dl) HS	IS
0	44±13	47±5	305±29	304±16	138±5	137±5	37±6	35±5	6.5±0.6	5.9±0.7
15	§82±13	58±9	*332±31	308±15	146±6	138±5	32±6	35±5	5.4±0.7	5.7±0.6

HS vs IS significantly different: § $p < 0.001$; * $p < 0.05$.

126 ENHANCED MUSCLE AND LIVER PROTEIN SYNTHESIS WITH MODIFIED DAIRY FAT (MDF) IN ENTERALLY-FED BURNED RATS. S.J. DeMichele, M.D. Karlstad, B.R. Bistrian, N. Istfan, V.K. Babayan and G.L. Blackburn. Nutrition Metabolism Laboratory, New England Deaconess Hospital, Harvard Medical School, Boston, MA 02215.

Previously we showed that enteral administration of chemically rearranged fats reduce net protein catabolism after thermal injury. The effect of different types of fat on protein metabolism was assessed in enterally-fed burned rats (25-30% BSA) given either long- (LCT) and medium-chain triglycerides (MCT) or MDF (36% C8-12: 64% C14-18) composed of a transesterified mixture of MCT (35%), butter (50%) and sunflower (15%) oil. Male Sprague-Dawley rats (200g) received 50 ml/day containing 50 kcal, 2 g amino acids and 40% nonprotein calories as fat for 3 days. Muscle and liver fractional synthetic rates (FSR, %/day) and ratios of tissue breakdown to synthesis (BRK/SYN) were estimated using a 4 hr constant IV infusion of [1-14C]-leucine on day 3. Mean (+ SE) values for cumulative nitrogen balance (CNB, mgN/day 2 + 3), serum albumin (g/dl), muscle and liver FSR and BRK/SYN are shown below:

Group	n	CNB	Serum Alb.	Mus FSR	Liver FSR	Mus BRK/SYN	Liv BRK/SYN
LCT	9	-12 ± 9	2.2 ± 0.1	2.4 ± 0.1	31.1 ± 3.4	1.05 ± 0.08	1.06 ± 0.09
MCT	8	-29 ± 20	2.9 ± 0.1b	2.6 ± 0.1	28.8 ± 1.7	0.98 ± 0.11	1.00 ± 0.07
MDF	8	+41 ± 14a	2.7 ± 0.1b	3.2 ± 0.3c	51.9 ± 2.6a	1.07 ± 0.10	0.59 ± 0.04a

a=P<0.01, MDF vs LCT and MCT; b=P<0.01, MDF and MCT vs LCT; c=P<0.05, MDF vs LCT. MDF had greater CNB and Mus and Liver FSR than either LCT or MCT. MDF and MCT maintained higher serum albumin levels than LCT. Liv BRK/SYN ratio was notably more anabolic than LCT or MCT. MDF, as a unique energy source, was superior to either LCT or MCT in improving protein metabolism following thermal injury.

127 PLASMA CATECHOLAMINE LEVELS AFTER VARIABLE HEMORRHAGE SCHEDULES IN THE RAT. SA HAMBURGER and DP HENRY* Indiana University School of Medicine and Lilly Laboratory for Clinical Research, Indianapolis, IN 46202.

The effect of the intensity and duration of blood loss on sympathetic function was evaluated by sequentially measuring plasma norepinephrine (NE), epinephrine (E) and dopamine (DA) in urethane (1.3 gm/kg, IP) anesthesized rats. After a 30 min stabilization period, animals (n=8/group) were acutely bled either mildly (0.5 ml), moderately (1 ml/min for 5 min) or severely (1.2 ml/min for 5 min) and then all were bled chronically (0.5 ml) at 0.5, 1, 2 and 4 h. Others were bled massively (1 ml/min until death). Controls were bled (0.5 ml) acutely and at 4 h. Initial plasma levels of NE (793 ± 95 pg/ml), E (684 ± 150 pg/ml) and DA (218 ± 40 pg/ml) changed depending on the hemorrhage (hem) protocol. Mild hem elevated NE and E late (2 and 4 h) but DA levels were unchanged. With moderate hem, the elevation of E at 0.5 h preceded the NE and DA increases at 1 h. Severe or massive hem elicited an immediate (2 min) rise in E. After severe hem plasma E plateaued by 0.5 h (3556 ± 863 pg/ml) while after massive hem plasma E continued to rise (64973 ±14692 pg/ml at 10 min). Plasma NE was elevated later; 1 h after severe hem and 8 min after massive hem. Elevation of DA (528 ± 126 pg/ml) occurred 0.5 h after severe hem but DA was unchanged after massive hem. During massive hem, two phasic tachycardic episodes occurred correlating with the separate elevations of plasma E and NE. Tissue content of NE, E and DA was also determined. These studies demonstrate that alteration of intensity and duration elicit different patterns of plasma NE, E and DA. Plasma E may be an early indicator of the severity of hem. Funded in part by an AHA Fellowship, Indiana Affliate, Inc.

128 ALTERATIONS IN CEREBRAL BLOOD FLOW FOLLOWING RESUSCITATION FROM HEMORRHAGIC SHOCK AND AN INTRACRANIAL MASS LESION. J. Kane*, J. Geiser*, J. Barrett, D. Lange*, A. Robin*, and O. Jonasson*. Cook County Hosp. & Univ. of Ill., Chicago, IL. 60612

This study was undertaken to determine the influence of fluid resuscitation using 3% NaCl (HS), 0.9% NaCl (NS), or Dextran-40 (D-40), on cerebral blood flow (CBF). Using a hemorrhagic shock dog model with a standard artificially produced intracranial mass lesion, the beagle dogs were anesthetized and mechanically ventilated. A 4 cc inflatable balloon was placed epidurally in the left hemicranium and a subarachnoid bolt was placed for intracranial pressure (ICP) measurements in the right. Swan Ganz and arterial catheters were secured and after balloon inflation, the dogs were bled 40% of their blood volume. Resuscitation was initiated with a portion of their blood followed by either HS(n=4), NS(n=6), or D-40 (n=4) equal to the volume of shed blood. Using a radiotracer microsphere technique with four different isotopes, CBF was studied. ICP at baseline (BL), balloon inflation (BI), and end

shock (ES) were 8.7 ± .9 mmHg (SE), 22.9 ± 1.6, and 10.4 ± 1.2 respectively for all dogs. ICP increased significantly one hour following resuscitation with NS(35.5 ± 7.6, p<.01, paired) and D-40 (51.3 ± 7.4 p<.01, paired) but remained essentially unchanged with HS(17.3 ± 5.6, ns, paired; p<.05 vs NS, p<.01 vs D-40). CBF at BL and ES were 27.1 ± 2.4 ml/100g/min and 29.3 ± 3.0 respectively. CBF increased following resuscitation with NS by (9.2 ± 7.3, ns, paired) and D-40 by (14.8 ± 6.1, p<.05, paired) but was most striking with HS resuscitation (66.3 ± 20.0, p<.025, paired; p<.025 vs NS, p<.025 vs D-40). Resuscitation with HS in this model, enhances CBF significantly as compared to NS or D-40.

129 ALTERATIONS IN PROTEIN AND ENERGY METABOLISM IN THE THERMALLY INJURED RAT. M.D. Karlstad, S.J. DeMichele, B.R. Bistrian and G.L. Blackburn. Nutrition Metabolism Lab., New England Deaconess Hospital, Harvard Medical School, Boston, MA 02215.

The effect of thermal injury on protein and energy metabolism was investigated using a controlled enteral feeding rat model. Male Sprague-Dawley rats (200 g) received a 15 second dorsal scalding injury (25-30% BSA) and were gastrostomy-fed isovolemic (50 ml/day) diets that provided 60 kcal/day and 2.4 g amino acids/day for 3 days. Control rats were similarly fed but were not burned. Muscle and liver fractional synthetic rates (FSR) and plasma leucine (leu) clearance were estimated using a 4 hr constant intravenous infusion of [1-14C]leu on day 3. Mean (±SE) values for cumulative nitrogen balance (CNB, mgN/3 days), total energy expenditure (TEE, kcal/kg/day), muscle and liver FSR (%/day), plasma [leu] (umol/ml) and plasma leu clearance (PLC, ml/100g/hr) are shown below:

Group	n	CNB	TEE	Mus FSR	Liver FSR	Plasma [Leu]	PLC
Control	7	383 ± 22	144 ± 6	5.0 ± 0.4	19.0 ± 0.5	0.148 ± 0.006	238 ± 11
Burned	9	120 ± 14**	169 ± 5**	3.5 ± 0.5*	39.2 ± 3.4**	0.178 ± 0.007**	203 ± 5*

n = no. of rats; * P < 0.05 and ** P < 0.01 compared to control (Student's t-test)

There was a 17% increase in TEE and a 69% reduction in CNB with a 30% decrease in muscle FSR and a 106% increase in liver FSR in burned rats. A 15% decrease in PLC was accompanied by a 20% increase in plasma [leu] with burn injury. These changes are consistent with a hypermetabolic response to injury. Such a controlled feeding model can be useful in the design of diets that minimize protein catabolism and support protein synthesis after injury.

130 A SIMPLE COAGULATION ASSAY IN THE ASSESSMENT OF TRAUMA SEVERITY. J. McCullough*, C. Spillert, and E. Lazaro*. UMD-New Jersey Medical School, Newark, NJ, 07103-2757.

The Injury Severity Score (ISS) is a commonly used index of the seriousness of a traumatized patient's injuries. To compare equivalent injuries in different age groups the ISS can be expressed as a percentage of the 50% lethal dose of injury for that age group ($\%LD_{50}$). We have previously shown that the decrease in whole blood recalcification time (RT) seen following E. coli endotoxin (ECE) stimulation is indicative of monocyte activation. The purpose of this study was to determine if there is any correlation between the ISS expressed as $\%LD_{50}$ and monocyte activation as measured by shortening of the RT. Within 48 hrs. of admission 2 ml of citrated whole blood (CWB) was obtained from 15 traumatized patients. Each patient's ISS and $\%LD_{50}$ was calculated (range: 3%-85%). Each CWB sample was divided into 2 one ml aliquots with 10 µg of ECE (Difco) being added to one sample, and 20 µl of saline to the other, followed by a 2 hour incubation at 37°C. 200 µl of each was then added to 100 µl of 0.04M $CaCl_2$ and the RT was determined on a Hepcon B10. The difference in the RT between each patient's samples was calculated as percent shortening. The correlation coefficient between $\%LD_{50}$ and percent shortening of the RT was 0.769 ($p<0.01$). This study demonstrated that the magnitude of the monocytes response to ECE stimulus is significantly and directly correlated with the severity of a traumatized patient's injury.

131 THE EFFECT OF DIFFERENT DEGREES OF HYPOTHERMIA ON THE MYOCARDIUM IN THE TREATMENT OF HEMORRHAGIC SHOCK(HS). Dan M. Meyer* & Jureta W. Horton. University of Texas Health Science Center at Dallas, Southwestern Medical School, Dallas, Texas.

Use of hypothermia(HYPO) in cardiac and neurological surgery is well established; its use in treating HS is controversial. Using a modified Wiggers' HS model, we

studied effects of HYPO on dogs (Group 1, 33°C, N=7; Group 2, 28°C, N=12) after the onset of HS. Control dogs (Group 3, N=6) were maintained at normal body temperature in HS and resuscitation. 60 min after resuscitation (shed blood and lactated Ringer's) dogs were rewarmed and studied for 120 min. Results revealed lower heart rate (beats/min) (80.6±3.3*, 62.5±4.1* vs 136.7±4.2*), negative rate of left ventricular pressure rise (-dP/dt, mmHg/sec) (938±125*, 700±75* vs 1550±275*), pH (7.15±.02*, 7.10±.03* vs 7.24±.02*), respiratory rate (18±1*, 14±1* vs 24±2*) and a higher pCO_2 (36.6±1.6*, 46.9±4.6* vs 20.3±2.0*) during HYPO HS in Group 1 and 2 when compared to Group 3, respectively. A lower LVEDP (mmHg) and cardiac output (L/min) was noted in Group 2 when compared to Group 1 and 3 (2.12±.5* vs 4.7±.7*, 5.3±.8*, and 1.14±.1* vs 1.45±.1*, 1.53±.2*, respectively), while dP/dt remained stable. A higher myocardial oxygen consumption and a negative myocardial lactate balance occurred in Group 3. After resuscitation, a higher stroke volume (ml) was seen in Group 2 when compared to Groups 1 and 3 (41.1±3.1* vs 35.9±3.25, 26.7±4.2*). With rewarming all measured parameters approached baseline. Results suggest a deeper level of HYPO decreases metabolic needs and enhances myocardial contractile function in HS. Both levels of HYPO have a protective and beneficial effect on the heart, and a possible role in treating HS. (*Indicates $p<0.05$)

132 COMPARISON OF CENTRAL AND PERIPHERAL HEATING ON SURVIVAL IN HEMORRHAGIC SHOCK. A.J. SORI*, A. EL-ASSUOOTY*, B.F. RUSH,JR., and J. HSIEH*, DEPARTMENT OF SURGERY, UMD-NEW JERSEY MEDICAL SCHOOL, NEWARK, N.J.,07103

In a resuscitated model of hemorrhagic shock in rats, where 11 of 12 animals were alive to 4 hours after shock, there was an average drop of 10 C in core body temperature. Survival and morbidity was much impaired when the shocked animals were externally heated to maintain a core body temperature of 35 C. Since the increased intrashock mortality is possibly due to the circulatory changes induced by peripheral heating, we attempted to determine the effects of heating the animal at its core. Twelve rats were shocked in the same fashion, however the body core temperature was maintained between 34 and 36 C, using 2450 MHz microwave radiation which penetrates 2 cm into tissue before conversion to thermal energy.

	END OF SHOCK	2HRS	4HRS	24HRS	36HRS	48HRS
MICROWAVE HEATING	4/12	4/12	4/12	1/12	1/12	1/12
EXTERNAL HEATING	5/11	3/11	2/11	1/11	0/11	0/11
HYPOTHERMIC	11/12	11/12	11/12	7/12	5/12	2/12

Initial BP, final BP, and total blood shed were the same for surviving animals at the end of shock in all groups. Survival was signifigantly better in the hypothermic animals ($p<.015$), and there was no signifigance between either heated group. Animals tolerated shock for 5 hours in the hypothermic group and only 2.5 hours in the microwave group($p<.01$).

133 CRITICAL OXYGEN DELIVERY IN SHOCK - EFFECTS OF OXYGEN AND FLUROCARBONS. N.S. Faithfull* and S.M. Cain. Dept. Physiology, Univ. Alabama at Birmingham,AL,USA. *Presently at Dept. Anaesthesia, Univ. Manchester, UK.

Haemodilution with Flurosol-DA 20%(FDA), an oxygen(O_2) carrying plasma substitute containing flurocarbons (FCs), can improve tissue oxygenation during ischaemic hypoxia. To determine the effect of FDA on critical oxygen delivery level (QO_2c), 2 groups of 6 phenobarbitone anaesthetised air ventilated splenic clamped mongrel dogs were haemodiluted to a haematocrit (Hct) of 25% with FDA or 6% detran solution. On line oxygen consumption(VO_2) was obtained from expired oxygen analysis and whole body O_2 flux(QO_2) was calculated from mixed venous and arterial O_2 contents and Fick derived cardiac output. Two further groups were similarly haemodiluted and ventilated with 100% O_2; VO_2 in these groups was obtained by spirometry. QO_2 was decreased by bleeding in 1.5-2.5 ml per kg steps. QO_2 was estimated at each step and Hct was kept at 25% using packed cells. VO_2/QO_2 pairs were calculated at each step and QO_2c was determined for each animal by fitting 2 lines through the data obtained using the least squares method. Statistical analysis was assessed using an analysis of variance. QO_2c was significantly less in the FDA+O_2 (F+O) group than either the dextran+O_2 (D+O) or detran+air (D+A) groups. Analysis of O_2 extraction (OE) at QO_2c, normalised for differences in resting VO_2, revealed significantly better OE in the FDA+air group (F+A) than in the D+A group. When FC and plasma dissoved oxygen was subtracted, OE in the F+A group was significantly better than in the D+A and F+O groups. The results imply that FDA haemodilution while respiring air can improve O_2 delivery from the red cell. Breathing 100% O_2 interferes with this process.

134 ROLE OF HISTAMINE IN SMALL ARTERIOLE DILATION DURING HYPOXIA. N. Alsip*, P. Harris, & E. Asher. Depts. Physiol & Anesthesiology, Univ Louisville, Louisville, KY 40292.

Large (A1) arterioles (90-150 μm diameter) constrict and small (A3) arterioles (6-30μm) dilate in skeletal muscle during hyperdynamic sepsis and hemorrhagic shock. These same microvascular responses also occur during systemic hypoxia to suggest hypoxia involvement in the microvascular responses to sepsis and/or hemorrhage. Small A3 dilation during hypoxia can be prevented by cyproheptadine, a non-specific anti-histaminergic and anti-serotonergic antagonist. Thus, serotonin or histamine could mediate small A3 dilation during hypoxia. To test this last idea, male rats were anesthetized (pentobarbital, 50 mg/kg subc.) and the cremaster muscles (with intact nerve and blood supplies) were submersed in a Kreb's bath with regulated pH, PO_2, PCO_2, and temperature. Large A1 and small A3 diameters (as % of baseline (BL) during 20% inspired O_2) were obtained during systemic hypoxia (HYPOX 10% inspired O_2), before and after bath addition of either methysergide (MYS 10^{-7}M, n=6) a serotonin antagonist, or diphenhydramine (DPH 10^{-5}M, n=6) a histamine antagonist.

	BL (n=6)	HYPOX	HYPOX + MYS	BL (n=6)	HYPOX	HYPOX + DPH
A1	108 ± 5μm	71 ± 5%	74 ± 6%	93 ± 5μm	76 ± 7%	72 ± 5%
A3	14 ± 1μm	163 ± 9%	158 ± 10%	11 ± 1μm	195 ± 15%	92 ± 14%*
BP	104 ± 5mmHg	49 ± 3%	56 ± 4%	112 ± 7mmHg	47 ± 4%	46 ± 4%

Large A1 constriction to hypoxia does not involve serotonergic or histaminergic receptors. Small A3 dilation during hypoxia does not depend on serotonergic receptors; however, hypoxia-induced A3 dilation appears to be mediated (*) by histaminergic receptors. (Kentucky Heart, AI22098).

135 EFFECT OF INDOMETHACIN ON HISTAMINE-INDUCED INCREASED ENDOTHELIAL CELL LAYER PERMEABILITY. R.Maier and C.Soderland*. Harborview Med Ctr; U of WA, Seattle, WA 98104

Permeability of the pulmonary microcirculation involves modulation of the endothelial cell (EC) barrier by inflammatory cell mediators, e.g. histamine or vasoactive prostanoids. Pretreatment with indomethacin (INDO) ameliorates inflammation-induced lung injury through a postulated inhibition of prostanoid release from inflammatory cells. In this study, the direct effect of INDO on histamine-induced EC barrier dysfunction was evaluated. Confluent rabbit pulmonary EC on microcarrier beads blocks the uptake of Evans blue dye by the beads. Parallel cultures of EC-covered beads were treated as control, glucose-glucose oxidase (G.O. 10 mU), or histamine (HIST 10^{-7}M) ± INDO (10^{-6}M) pretreatment for 2 hours, aliquots were obtained, and the remainder of the culture rinsed after sedimentation of the beads and allowed to recover for an additional 20 hours. Typical dye uptake is given:

TREATMENT	CONTROL	G.O.	HIST	HIST+INDO
2 hour	100%	209%	225%	137%
20 hour	100%	104%	227%	---

Both glucose oxidase-generated oxygen radicals and histamine induce a significant increase in the permeability. This was reversible for glucose oxidase, but not histamine. INDO inhibited the histamine effect. The protective effect may be inhibition of endogenous production of prostanoids by EC. Importantly, the protective effect of INDO in vivo may well not depend on the ability to block the release of vasoactive prostanoids by inflammatory cells.

136 PENTOBARBITAL ATTENUATES ARTERIOLAR CONSTRICTOR RESPONSES TO HEMORRHAGE. K. Offenbartl*, L.Flint SUNY-Buffalo, NY 14215

Hypothesis: Pentobarbital (PB) anesthesia alters microcirculation responses to hemorrhage [H]. Mechanisms are unclear. We studied effects of IVPB on constrictor responses (CR) of skeletal muscle (cremaster) arterioles to norepinephrine (NE) after mild [H] (10% blood volume). Rats were anesthetized with PB (50 mg/kg IP); made cortically insensate by a stereotactic precollicular brainstem transection and after 6 hr. recovery, muscles were suspended in a temp, pH and O_2 controlled Krebs bath. Control diameters (CD) of progressively smaller arterioles (A1,2,4) were recorded by videomicroscopy (1500X). Dose-response curves for NE were measured and a concentration of $3x10^{-8}$M NE chosen to assess CR at baseline (CRB) and after H [HR] or reinjection of PB (10% initial dose IV) plus H (HPB). Diameters and CR (expressed as -% CD, mean+/- SEM and adjusted for [H] induced constriction) are tabulated. Each vessel was its own control. Lumen reduction of 37% vs. CD=-37.

	CD (micromtr):	N	CRB	N	[HR]	N	(HPB)
A1	105+/-5	27	-38+/-3%	10	-42+/-7%	10	-26+/-8%
A2	47+/-2	20	-44+/-4%	7	-49+/-8%	6	-35+/-10%*
A4	17+/-1	46	-74+/-5%	16	-79+/-13%	16	-59+/-7%**

*$p < 0,05$ **$p < 0,02$ by paired t-test.

Conclusion: PB, even a 10% anesthetizing dose reduces CR of A2 and A4 arterioles to NE after mild hemorrhage. These observations help to explain inconsistent microcirculation responses to shock in anesthetized rats.

137 CHANGES IN CEREBRAL REGIONAL BLOOD FLOW AND TISSUE OXYGEN TENSION IN SHOCK AND BRAIN ISCHEMIA. K.Okada, O.Moritsune*, Y.Kikuta*, S.Tezuka*, H.Kawabata*, T.Ito* and K.Kajiyama*. Teikyo University, Tokyo 173, Tokyo Medical and Dental College, Tokyo Police Hospital, Tokyo, Japan

The effects of hemorrhage and ischemia on cerebral regional blood flow and cerebral tissue PO_2 were studied in dogs in an attempt to understand better the pathophysiology of shock and ischemia. Adult mongreal dogs were anesthetized with N_2O-O_2-enflurane and mechanically ventilated with a volume ventilator. Hemorrhage was controlled by maintaing arterial blood pressure at 50mmHg. Cerebral ischemia was induced by clamping both aortic arch and central veins. Heart did not stop beating during this period, and 5 or 10 minutes later these clamps were released. Cerebral regional blood flow was measured by hydrogen clearance method, and cerebral tissue PO_2 (P_tO_2) was measured with a fine Clark type needle. These blood flow and PO_2 sensors were placed on cortex and into medulla. Both P_tO_2 and tissue blood flow were decreased during hemorrhage, and the magnitude of decrease was variable, depending upon the level of blood pressure and the duration of hemorrhage.The amplitude of the decrease in P_tO_2 and regional blood flow was not the same in cortex and medulla. After retransfusion, P_tO_2 and regional blood flow were recovered. In ischemic model, P_tO_2 and regional blood flow were abruptly decreased in ischemic period. In declamping period, a difference of recovery in P_tO_2 and regional blood flow was found between cortex and medullar portion. It is suggested that autoregulatory mechanism might be disturbed much more in ischemia than in hemorrhage.

138 RENAL SYMPATHETIC AND PHRENIC NERVE ACTIVITIES DURING HEMORRHAGIC SHOCK IN RABBIT. S. Koyama, M. Aibiki, K. Kani and K. Miyakawa. Dept. of Physiology, Division 2, Shinshu University School of Medicine, Matsumoto, Nagano 390, Japan.

We studied time course changes in both phrenic nerve (PNA) and renal sympathetic nerve activities (RNA) during hemorrhagic shock in anesthetized rabbits. Systemic blood pressure, heart rate (HR), PNA and RNA were simultaneously measured on a multichannel recorder. Hemorrhagic hypotension of 20-30 mmHg was maintained by using a servo-controlled system. HR response to hemorrhage appeared as an initial increase (from 240 to 350 beats/min) followed by a decrease (to 180 beats/min at 5 min). Hemorrhage caused a significant increase in RNA at an initial stage (150% of control level), which was dependent on an activation of peripheral baroreceptor systems. There followed a secondary decline (18% of control level at 8 min). These profound decreases in RNA reached near the noise level and were maintained at this level until retransfusion. Simultaneously with these decreases in RNA, PNA responses showed a biphasic pattern: significant increases in PNA followed by a decrease to the near noise level. During this transitional period between increase and decrease in the activity, PNA showed irregular bursting. This reduction of PNA also recovered when shed blood was retransfused. The similar time course responses to hemorrhage on RNA and PNA occurred when total brain ischemia was made in the animals. Thus, these data may suggest that when hemorrhagic hypotension was prolonged, the results from the experimental model of hemorrhagic shock should be evaluated on the basis of time-dependent factors, mediated via the central nervous system.

139 **EXTRAVASCULAR LUNG WATER AFTER 24-HOURS TRAUMATIC-HEMORRHAGIC SHOCK IS INDEPENDENT UPON PRIMARY VOLUME REPLACEMENT.** M. Albrecht*, L.-G. Hein*, U.B. Brückner*. Dept. Exp. Surg., Univ. Heidelberg, 6900 Heidelberg/FRG.

The relevance of resuscitation modality for the development of shock-induced lung edema and ARDS is still controversial. Therefore, a study in dogs undergoing traumatic-hemorrhagic shock (MAP 40 mmHg, uptake 20%) was performed to answer the que-

stion: Do different volume substitutes influence the formation of lung edema? — Fourty anesthetized foxhound were randomized into five groups (8 animals each) for primary resuscitation with autologous blood and infusion of either 6% hydroxyethyl starch (HES, 450/0.7), 5% human serum albumin (ALB), 6% dextran-60 (DX), Ringer's lactate (RL), or 1.3% hyperosmolar saline (HS) with the aim to keep CO and CVP at pre-shock levels. Extravascular lung water (EVLW) and albumin accumulation (EVLA) were measured. All animals were treated and monitored for 24 hrs after shock. — To maintain pre-shock hemodynamics higher volumes (INF) of crystalloids ($p < 0.01$) were required. EVLW, however, increased ($p < 0.01$) to the same degree irrespective of the substitute used without amelioration during 24-hrs. Fluid loss (FL) into ascites and EVLA, respectively, were higher ($p < 0.01$) after therapy with crystalloids.

		HES	ALB	DX	RL	HS
INF	(ml/kg*h)	1.1 ± 0.3	1.8 ± 0.9	1.5 ± 0.6	6.8 ± 2.2	12.3 ± 3.2
EVLW	(ml/kg)	13.4 ± 2.7	12.9 ± 3.7	13.3 ± 3.7	13.9 ± 4.0	13.8 ± 2.4
FL	(ml/kg)	22.5 ± 8.1	28.1 ± 11.9	22.2 ± 6.7	48.5 ± 12.9	39.5 ± 12.1
EVLA	(%)	12.9 ± 3.8	12.3 ± 3.4	11.2 ± 1.7	17.9 ± 2.9	16.8 ± 2.8

In conclusion: (1) In our shock model the volume substitute did not influence the formation of early pulmonary edema. (2) Fluid loss into ascites was aggravated and (3) albumin extravasation was more pronounced in the crystalloid-treated animals.

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140 PULMONARY AND PERIPHERAL TRANSVASCULAR PROTEIN CLEARANCE FOLLOWING ACUTE SUBLETHAL PSEUDOMONAS BACTEREMIA. W. Charash*, T. Saba, E. Lewis* and M. Lewis*. Albany Medical College, Albany, NY 12208.

Multiple organ failure is common with sepsis following surgery, trauma and burn. The chronic sheep lung lymph fistula preparation has been used to detect pulmonary microvascular injury as reflected by protein clearance following bacteremia, endotoxemia and burn. Whether the increased vascular permeability is organ-specific or generalized is undefined. We studied the effect of post-operative bacteremia on both lung and peripheral protein clearance using unanesthetized sheep with both pulmonary and pre-femoral lymph fistulae. Baseline lymph to plasma total protein ratios (L/P) were 0.63± 0.09 and 0.43±0.06 in pulmonary and peripheral beds, respectively. Baseline L/P fibronectin ratios were 0.39±0.09 and 0.16±0.05 in pulmonary and peripheral beds, respectively. Sheep (n=3) received live *Pseudomonas aeruginosa* ($5x10^8$ i.v.) over a 1 hr infusion and were studied for 48 hrs. Pulmonary lymph flow (Q_L) increased by 2 hrs with an associated decline in L/P total protein. A second phase response over 3-12 hrs was characterized by an increase in both Q_L and L/P ratio, yielding an increased transvascular protein clearance ($TVPC=Q_L \times L/P$) as previously reported. Pre-femoral lymph flow (4.9 ml/hr), L/P total protein and TVPC (2.0 ml/hr) did not rise during the 48 hr period. Thus, the molecular sieving ability of the peripheral microvasculature is greater than the pulmonary microvasculature. It is also more resistant to low level post-operative bacteremia. This suggests that pulmonary edema may develop prior to peripheral edema in post-operative sepsis. (GM21447; GM07033)

141 THE RELATIONSHIP BETWEEN PULMONARY INJURY AND PRODUCTS FROM ISCHEMIC INTESTINE DURING SHOCK PROCESS. F. CHEN*, C. TANG* AND J-Y SU*. (Spon: M-S LIU). Dept. of Pathophysiology, Beijing Med. Univ., Beijing, P.R. China.

This work investigated the possible relationship between shock intestine and lung function during shock. Superior mesenteric artery occlusion (SMAO) shock was produced on rabbits. SMA was occluded for 1h and on releasing of the artery MABP decreased abruptly, 100% of the animals died within the following 4h. Arterial blood O_2 pressure (PaO_2) was measured before occlusion and every 60 min after release of the occlusion. Control animals endured the same operation with no SMAO. There is no declination of PaO_2 in the SMAO shock group while MABP showed significant decrease. But pulmonary capillary permeability index (PCPI= protein in bronchial lavage/plasma protein) was significantly higher in the SMAO group(n=10, than in control group(n=8), $p<0.01$. In the further experiments blood was collected from SMV after 1h SMAO in cats. The plasma of this SMV blood was used for isolated rat lung perfusion (38°C,45 min,flow rate 10ml/min). Pulmonary arterial pressure(PAP), PCPI, the product of lipid peroxidation MDA,and LDH in the perfusion fluid were measured prior to and after the perfusion period. The changes in these parameters were more prominant in the expt. group(n=9, vs control group(n=8,: PAP 26.6±0.9 vs 21.4±0.8 mmHg($P<0.01$), PCPI 0.027±0.013 vs 0.019±0.003($P<0.05$), MDA increase 44.8±6.9% vs. 13.6±7.9%($P<0.02$), LDH 0.24±0.07 vs 0.08±0.04 Becker's unit($P<0.01$). These changes occurred prior to the declination of PaO_2. Results indicated that products from ischemic intestine have definite deleterious effect on lung functions.

142 SEVERE RESPIRATORY FAILURE AFTER NONPENETRATING MULTIPLE TRAUMA: AN UNCOMMON PROBLEM. Mitchell P Fink, Department of Surgery, University of Massachusetts Medical Center, 55 Lake Avenue, Worcester, MA 01605.

I reviewed the charts of all adult nonpenetrating trauma patients admitted during 1985 to the Surgical Intensive Care Units at a major Level I referral center. Patients (N = 14) that died within 48 h of admission were excluded from the analysis. All but one of the patients in this excluded group died as a direct result of overwhelming head injuries. For the remaining patients (N = 172), the median values for age, injury severity score (ISS), and APACHE-II score were 28, 26, and 7, respectively. Severe respiratory failure ($PaO_2/FIO_2 \leq 140$ on at least 2 successive arterial blood gases) occurred in 16 patients (9.3%). Moderate respiratory failure ($PaO_2/FIO_2 \leq 180$ on at least 2 successive arterial blood gases) occurred in 12 patients (7.0%). Only 14 patients (8.1%) required 15 or more cm H_2O of PEEP. Only one patient died as a direct result of respiratory failure. Development of respiratory failure correlated with chest trauma ($p = .011$), thoracotomy ($p < .001$), number of lower extremity plus pelvic fractures ($p = .044$), number of transfused units during first 24 h ($p = .006$), systolic blood pressure $\leq$ 80 mm Hg during first 24 h ($p = .002$), ISS ($p = .004$), and APACHE-II score ($p < .001$). These data indicate that (i) severe respiratory failure is a surprisingly uncommon problem in severely injured victims of nonpenetrating trauma; (ii) oxygenation failure per se is rarely the cause of death in this population.

143 BIOCHEMICAL MONITORING OF THE LUNG DURING EXTRACORPOREAL CIRCULATION (ECC). G. Horpacsy, W. Hügel*, H. Müller*, I. Schnells*, R. Küppers*.
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The activity of N-acetyl-beta-glucosaminidase (NAG), lysozyme and PMN-elastase has been investigated in the superior vena caval and left atrium blood collected from 167 patients who underwent open heart surgery. The effect of various types of respiration on the enzyme release has been also documented. Concentration gradients between v. cava sup. and left atrium has been used as an index for pulmonary damage during ECC and post operatively. We found a time dependent increase of all enzymes during extracorporeal circulation. However, only the release of NAG and lysozyme is characteristic for pulmonary damage. We observed significantly higher enzyme release from the lung after Apnoe ventilation compared with the PEEP and low frequency ventilation group. Also significantly higher NAG and lysozyme activity were found in patients who needed longer respiration post-operatively. PMN-elastase seems to be not suitable for diagnosis of post perfusion lung because the main amount of elastase is released by mechanical destruction of the granulocytes. The biochemical monitoring of "post perfusion lung" by measuring enzyme activities completes the other diagnostic procedures such as the determination of lung water content. The determination of lysosomal enzymes gives early information about the degree of pulmonary damage and recovery of lung function post-operatively.

144 ENDOTOXEMIA AND SYSTEMIC COMPLEMENT ACTIVATION IN THE CONSCIOUS SHEEP. G. JESMOK,* D. CHENOWETH,* R. VIRAY, J. BORGIA*, Travenol Laboratories, Inc., Round Lake, IL 60073

The mechanism(s) whereby intravenous endotoxin elicits an intravascular inflammatory reaction is not presently known, but may involve activation of circulating complement. We examined this hypothesis in conscious sheep with lung-lymph fistula (N = 5) by direct measurement of plasma levels of ovine C3a following intravenous endotoxin (E. coli 055:35 1 µg/Kg over 10 min) administration. Plasma samples for C3a measurements (radioimmunoassay) were taken at 10 min intervals during the first hour after endotoxin injection and at 30 min intervals for an additional four hours. Endotoxin induced the well-characterized ovine cardiopulmonary response, i.e., an early phase (10-50 min) of pronounced pulmonary and systemic vasoconstriction and a later phase (60-300 min) of elevated flow (4-5 fold) of protein rich pulmonary lymph. These changes were accompanied by a decline in circulating granulocytes (20-300 min). Control C3a levels prior to endotoxin infusion were 366 ± 66 ng/ml. Subsequent quantitation demonstrated that circulating C3a levels were not significantly elevated at any time point after endotoxin administration. Representative values (ng/ml) were 30 min, 397 ± 70; 60 min, 492 ± 97; 120 min, 460 ± 113; 180 min, 491 ± 36; 300 min, 453 ± 97. These results suggest that intravenous endotoxin (1 µg/Kg) may induce alterations in cardiovascular and granulocyte status without significantly activating the ovine complement system.

145 BRONCHOCONSTRICTOR AND PULMONARY VASOCONSTRICTOR EFFECTS OF OXYGEN FREE RADICALS (OFR): DIFFERENT MECHANISMS? J.Kjæve*, T.Ingebretsen*, L.Næss*, J.Vaage and L.Bjertnæs*. Depts. of Anesth. and Surg., University of Tromsø, Tromsø, Norway.

The parallel airway and vasoconstrictor effects of OFR as well as possible modulating effects of methylprednisolone (MP) and catalase (CAT) were investigated. Isolated rat lungs were perfused with horse plasma at constant volume inflow (15 ml/min) and ventilated with air containing 5% CO_2 (60 breaths/min, tidal volume 3 ml). In the control group xanthine oxidase (XO)(5 units) and hypoxanthine (HX)(1 mM) were added to the perfusate. In separate groups CAT (20 mg) or MP (20 mg) were also added in addition to XO+HX. Baseline perfusion pressure (all groups pooled) was 7±0,3 mmHg, and baseline transpulmonary pressure (all groups pooled) 2±0,2 cmH_2O. All values are evaluated as per cent of the baseline value (before XO+HX) and given as mean ±SEM.

	Pulmonary arterial pressure				Transpulmonary pressure			
Time after XO+HX	5 min	15	30	60	5	15	30	60 min
Controls (n=10)	131±3	194±11	271±25	243±25	151±10	154±10	168±12	190±19
+ MP (n=6)	115±2*	149±5*	177±16**	173±16	114±2*	118±6**	134±12	172±15
+ CAT (n=6)	130±5	210±11	179±14*	173±24	118±7*	124±8**	118±11*	135±17**

* p< 0,01, ** p< 0,03, (Wilcoxon two-sided test).

In conclusion, airways constrict concomitant with the pulmonary vascular bed. The different timing of the attenuating effects of CAT and MP suggest that the mechanisms constricting airways and lungs vessels may be different and change with time.

146 ALTERED PULMONARY MICROVASCULAR PERMEABILITY AFTER SEPSIS, OLEIC ACID AND PULMONARY TRAUMA. L. Smith*, S. Andreasson* and B. Risberg.
Dept. Surgery, Univ. Göteborg, S-413 45 Göteborg, Sweden.

The lung lymph fistula preparation in sheep was used to investigate the effect of a preparative trauma, infusion of live E. coli or oleic acid on lung microvascular permeability. The changes in permeability were characterized by the osmotic reflection coefficient (σ_d) and by equivalent pores as σ_d for 3 endogenous proteins (albumin, IgG and IgM) were calculated. Stable filtration independent lymph data at high lung microvascular pressure, achieved by elevation of left atrial pressure, were used for calculations. In control sheep (n=5) with chronic lung lymph fistula σ_d for total protein (TP) was 0.76±0.01 with equivalent small and large pores of 54 and 190 Å, respectively. After bilateral thoracotomies for lung lymph fistula preparation (n=9) or after infusion of live E. coli (10^9/Kg bw, n=7) the number of large unselective leakes increased with a reduction in σ_d to 0.61±0.01 and 0.58±0.04, respectively. Infusion of oleic acid (0.05ml/Kg bw, n=6) decreased σ_d to 0.29±0.07 for TP with an increase of the number and size of large pores. Thus, preparative trauma and sepsis altered permeability in a simililar way, whereas oleic acid damaged the microvascular membrane more severely as was also demonstrated by heavy pulmonary edema in these animals.

147 AIRWAY ACID INJURY FOLLOWING SMOKE INHALATION. J. Stothert, Jr., D. Herndon, L. Traber*, J. Flynn, R. Mecker*, D. Traber. UT Med Br and Shriners Brns Inst, Galveston, TX, 77550.

This study examines pulmonary injury following smoke inhalation and airway acid inhalation in an ovine model (single vs multiple pulmonary insults). All animals had previously fashioned chronic lung lymph fistulae and were fully instrumented with vascular monitoring catheters. Ten days following a standard cotton smoke injury, animals in the experimental group sa (n=9) were anesthetized and underwent airway acid aspiration using 0.1 N. hydrochloric acid (2.5cc/kg body weight). Control group aa (n=9) underwent acid aspiration alone. Results are listed below. Significance: *=p<0.05, **=p<.001 as compared to baseline by student's t-test.

	Baseline		2 HR		4 HR		48 HR	
	aa	sa	aa	sa	aa	sa	aa	sa
Lung lymph flow cc/hr	13.1	10.1	30.3**	36.0**	24.5*	34.0*	22.5*	19.1*
Lymph/Plasma Protein	.51	.56	.62	.67*	.62	.61	.59	.49
Thromboxane-lymph	0.2	0.5	1.8*	3.7*	0.6	1.1*	0.2	0.5
(ng/ml) plasma	0.2	0.7	0.3	0.7	0.4	0.7	0.3	0.9
Prostacyclin-lymph	0.4	0.6	7.2*	17.5**	2.4	9.6*	0.4	0.6
(ng/ml) plasma	0.4	0.7	0.4	1.21**	0.4	0.8*	0.4	0.8

These data suggest that the adverse response to acid aspiration is greater after previous smoke inhalation. The mechanism resulting in increased mediator release may be associated with the margination of WBC's in the lung after smoke inhalation. (Supported by NIH Grant #HL36452)

148 CONTINUOUS INFUSION OF ENDOTOXIN REDUCES THE CARDIOVASCULAR BUT NOT PULMONARY RESPONSE TO SINGLE BOLUS ADMINISTRATION OF THE LIPOPOLYSACCHARIDE (LPS). L. Traber*, D. Traber. Univ of TX Med Br and Shriners Brns Inst, Galveston, TX, 77550.

Septic patients typically show a continuous release of the LPS with additional pulses of material occurring periodically. We modeled this situation in the sheep. METHODS: Six sheep were surgically prepared and 7 days later baseline data collected and LPS (12 ng/Kg/hr) was begun. Twenty-four hours later, a single bolus of 1.5 ug/Kg was given and the animals studied for 24 hrs. The data were compared to sheep which received a single bolus of LPS without prior continuous infusion. RESULTS: LPS results in a biphasic response. An increase in lung lymph flow (LQ) associated with a marked increase in pulmonary artery pressure (PAP) with no change in permeability index (PI). During Phase II LQ is likewise elevated, but with an increase in PI and a mild rise in PAP. When LPS was administered following the 24 hour continuous infusion, the LQ response was reduced during both phases. During Phase I, the change in PAP was reduced while during Phase II the changes in PI were not as great. CONCLUSION: The pulmonary vascular response to LPS is reduced by reduced by prior administration as a continuous infusion.

		CONT	PHASE I	PHASE II
PI	C	3.6±0.6	4.9±0.5	16.8±3.4*
ml/hr	T	2.6±0.7	4.3±1.2	7.5±1.4
LQ	C	6.3±1.1	16.7±2.7*	23.8±4.1*
ml/hr	T	5.4±1.4	12.6±3.9	12.1±2.3
PAP	C	21±1	47±3*	27±2
mmHg	T	20±2.4	31±5.3	29±2

C=Control group - 1.5 ug only
T=1.5 ug Post 24 ng Infusion
*=$p<0.05$
(NIH Grant #HL34752)

149 EVALUATION OF THE INCREASED PULMONARY PERMEABILITY INDUCED BY OXYGEN FREE RADICALS (OFR). J. Vaage, J. Kjæve*, L. Næss*, T. Ingebretsen* and L. Bjertnæs*. Depts. of Anesth. and Surg., Univer. of Tromsø, Tromsø, Norway.

Pulmonary microvascular permeability is increased by OFR. We studied whether this was an acute, reversible or prolonged effect. The possibility of secondary, circulating mediators was also investigated. Isolated, ventilated rat lungs were perfused with horse plasma (recirculating) at constant volume inflow. Papaverine was added to maintain perfusion pressure constant. Group I: Controls. Capillary filtration coefficient (CFC) was studied after stabilization (CFC 0), and then after 30 (CFC 30) and 60 min (CFC 60) (n=5). Group II: Identical to group I, but xanthine oxidase (XO) and hypoxanthine (HX) were added to the perfusate after CFC 0 (n=6). Group III: Same as group II except that catalase was added before XO and HX (n=6). Group IV: Identical with group II until CFC 30, after which the perfusate was exchanged with fresh plasma (n=7). There was no significant change in CFC with time in groups I and III. In groups II and IV pooled together (n=13), CFC 0 and CFC 30 were 15±3 (mean ± SEM) and 80±11 mg/min respectively (p=0,0001, Wilcoxon two-sided test). In group II CFC increased further from 30 to 60 min (Δ CFC) by 31±7 mg/min ($p< 0,001$). However, in group IV Δ CFC was - 14±6 mg/min which was significantly different from group II ($p< 0,001$). In conclusion, OFR will increase microvascular permeability in isolated, perfused rat lungs. The increase with time is inhibited by changing the perfusate after 30 min, suggesting that secondary mediators circulating in the perfusate may cause the late increase in permeability.

150 A SIMPLE METHOD FOR RAPID ESTIMATE OF PULMONARY VENOUS ADMIXTURE. Carlo Chiarla*, Ivo Giovannini, John H. Siegel[1], Bill Coleman*[1], Giuseppe Boldrini*, Marco Castagneto. Centro di Studio per la Fisiopatologia dello Shock, CNR, I-00168 Rome, Italy and [1]MIEMSS and Departments of Surgery and Pathology, University of MD, Baltimore, MD 21201.

Mathematical relationships have been developed for simple determination of Pulmonary Venous Admixture (P.V.A.%) from arterial and central venous blood O_2 tensions (PaO_2 and $P\bar{v}O_2$, mm Hg) or saturations (SaO_2 and $S\bar{v}O_2$, %). The P.V.A. has been measured by adaptations of the Berggren method on the basis of arterial, central venous and pulmonary capillary blood O_2 concentrations. Regression analysis was performed in data from 2298 respiratory measurements performed in 733 surgical and trauma patients at inspired O_2 concentrations ($\%FIO_2$) between 21% and 100%. In spontaneously ventilating patients at FIO_2=21% the best fit was allowed by the following regression:

$$P.V.A.\% = 1036/(PaO_2-PvO_2)-4235/(PaO_2-P\bar{v}O_2)^2-12 \quad n=586 \quad r^2=.93 \quad p<.0001$$

At FIO_2's greater than 21% the best fit was obtained by the use of the O_2 saturations:

P.V.A.% = $-2.4(SaO_2)+.6\ (S\bar{v}O_2)+.25(\%FIO_2)+200$ n=1712 $r^2=.84$, $p<.0001$
These two formulas may be employed at the bedside for rapid calculation of P.V.A. and used to construct a multidimensional grid for instantaneous graphical determination of P.V.A. based on the same O_2 tensions or saturations.

151 **CATALASE PRETREATMENT ATTENUATES OLEIC ACID-INDUCED PULMONARY INJURY IN THE ISOLATED, PERFUSED RABBIT LUNG.** S.A. Katz*, J.A. Cook, J.E. Heffner*, P.V. Halushka, and W.C. Wise. Medical University of South Carolina, Charleston, SC 29425.

Intravenous injection of oleic acid (OA) induces profound pulmonary edema as a result of an increase in microvascular permeability. Experimental studies have demonstrated the potential involvement of oxygen-derived free radicals as mediators of acute, permeability lung injury. We tested the hypothesis that free radicals mediate, in part, the pulmonary injury induced by OA in the isolated, Krebs-perfused rabbit lung. Isolated lungs, ventilated with $95\%O_2/5\%CO_2$ and perfused with Krebs buffer, were pretreated with vehicle, Cu-tryptophan (40 μM, a lipid soluble scavenger of superoxide), or catalase (1000 U/ml, a scavenger of hydrogen peroxide) 15 min prior to injection of OA (0.1 ml).

TREATMENT	WT GAIN (gm)	AWP (mm Hg)	PAP (mm Hg)
Krebs/Vehicle (n=8)	2.2 ± 2.2*	10.9 ± 0.4*	17.3 ± 2.5
Krebs/OA (n=5)	50.4 ±13.9	15.0 ± 1.5	21.6 ± 2.5
Cu-tryptophan/OA (n=6)	43.8 ± 8.4	15.2 ± 0.7	18.8 ± 0.6
Catalase/OA (n=7)	15.1 ± 4.9*	12.0 ± 0.7*	14.3 ± 0.8*

AWP: Maximum airway pressure. PAP: Mean pulmonary artery pressure. Values are mean ± SEM 45 min post OA. *p<0.05 vs OA, 0 - 45 min by ANOVA.

These data demonstrate that OA induces pulmonary edema in the absence of blood components and that pretreatment with catalase, but not Cu-tryptophan, attenuates OA-induced edema. These results suggest that hydrogen peroxide is generated by OA embolism in the isolated, perfused rabbit lung and in part mediates the vascular injury in this system. (Supported by NIH GM-27673)

152 EFFECT OF ANISODAMINE ON GLUCOCORTICOID RECEPTOR (GCR) OF PULMONARY ALVEOLAR MACROPHAGE (PAM) IN RABBITS WITH OLEIC ACID (OA) INDUCED RESPIRATORY DYSTRESS SYNDROM (RDS). Zhengyao Luo*, Ling Xu*, and Han Luo* (Spon: M.S. Liu). Hunan Medical College, People's Republic of China.

The effects of anisodamine on GCR of PAM were studied using ^{3}[H]-dexamisone as a radioactive ligand and an intact cell binding assay. In addition, respiratory permeability index (RPI) and lung coefficiency were measured. Results are as follows (mean ± SEM):

		Control group (N = 9)	OA group (N = 16)	OA + Anisodamine group (N = 16)
Bmax (sites/cell)		15092±248	6442±841*	12075±633†
Kd (nM)		1.8±0.4	3.8±0.3*	2.2±0.4†
Bronco-Alveolar Lavage Fluid	PMN ($x10^7/mm^3$)	0.05±0.01	4.91±0.65*	3.01±0.46†
	RBC ($x10^9/mm^3$)	0.07±0.01	5.32±0.83*	2.61±0.26†
	Albumin (mg/ml)	0.02±0.01	0.38±0.03*	0.27±0.03†
	RPI	0.004±0.001	0.13±0.01*	0.09±0.01†
Lung Coefficiency		4.5±0.1	9.0±0.3*	6.8±0.3†

* Compared with control group p<0.05; † Compared with OA group p<0.05.

These results indicate that OA induced typical changes of RDS and these changes could be protected by anisodamine.

153 **MITOCHONDRIAL BIOCHEMICAL ALTERATIONS DURING HEMORRHAGIC SHOCK AND LONG-TERM SEVERE HYPOXIA IN DOGS.** G.G. Corbucci*, A. Gasparetto*, M. Antonelli*, M. Bufi* and R.A. De Blasi* (Spon: A.M. Lefer). Institute of Anaesthesia and Resuscitation, University "La Sapienza", 00161 Rome, Italy.

In an attempt to clarify some aspects of mitochondrial oxidative damage in long-term severe hypoxia and in the reversible phase of circulatory shock, we examined the activity of electrogenic carriers and the Krebs cycle oxidative capacities in two different experimental models. In a group of 7 dogs, we induced hemorrhagic shock and in another group of 7 dogs, we studied the hypoxic state induced by partial ligation of the femoral artery (80% of the artery lumen) for 4 hours. In both groups, skeletal muscle biopsies were taken at fixed time intervals and examined by spectrophotometric and HPLC methods.

The results obtained show a progressive and significant decrease of the electron carriers (i.e., cytochrome oxidase, succinate dehydrogenase, coenzyme Q_{10}) oxidative capacity and a parallel inactivation of the Krebs cycle dehydrogenases. The activation of oxy-radicals seems to represent a consequence of the oxidative damage, even if the peroxidative damage, measured by hydroxyl radical, vitamins C and E concentrations and superoxide dismutase activity appear to characterize the extent of the cell injury. The reversible phase of circulatory shock shows biochemical alterations similar to that observed in hypoxia in terms of the mitochondrial adaptive changes due to lower oxygen tension. Thus, the loss of mitochondrial adaptive capacity appears to characterize the passage to the irreversible phase of shock, which could be interpreted, from the biochemical point of view, as exhaustion of the adaptive response of the mitochondrial to hypoxia.

154 THE HEMODYNAMIC EFFECTS OF CALCIUM CHLORIDE IN HYPOCALCEMIC POSTOPERATIVE PATIENTS. S.R. Berger*, E. Benjamin, T.J. Iberti. Departments of Surgery & Anesthesiology, The Mount Sinai Medical Center, One Gustave Levy Place, New York, N.Y. 10029.

Hypocalcemia is often seen in critically ill surgical patients. Previous studies have been inconclusive as to whether there is any benefit in normalizing the ionized calcium. We studied 12 consecutive patients (mean age 70±9 yr) following non-cardiac surgical procedures, each with an ionized calcium of <1.09 mM/L. Heart rate (HR), mean pulmonary artery pressure (MPAP), mean arterial pressure (MAP), pulmonary capillary wedge pressure (WP), central venous pressure (CVP), and cardiac output (CO) were measured. One gram of calcium chloride was infused over 10 min and values repeated 15, 30, 60, and 120 min. Stroke volume (SV), left ventricular stroke work (LVSW), and systemic resistance (SVR) were calculated. The data were compared using analysis of variance ($p<0.05$ significant).

The mean ionized calcium level was 0.95 mM/L at baseline, and 1.1 at two hr ($p<0.05$). MAP, SVR, and LVSW were significantly elevated at 15 min. This apparent increase in afterload was present for less than one hr. A subsequent phase of depressed cardiac function was seen at 2 hr, characterized by decreased CO, SV, and LVSW. Thus, in this group of elderly, postoperative patients, treatment of ionized hypocalcemia did not improve cardiac function.

155 ANALYSIS OF HEMODYNAMICS AND BLOOD GAS IN RELATION TO BLOOD KETONE BODY RATIO IN PARTIALLY HEPATECTOMIZED PATIENTS. T.Nakatani*, Y. Shimahara*, K.Mori*, N.Kobayashi*, Y.Yamaoka*, K.Kobayashi*, K.Ozawa*(Spon: Y.Kamiyama) Trauma and Critical Care Center, Teikyo University, Tokyo, 173 Japan, and 2nd Dept of Surgery, Kyoto University, Kyoto, 606 Japan

Total number of 360 studies of hemodynamics and blood gas analyses were performed in 41 partially hepatectomized non-septic patients in relation to hepatic mitochondrial redox state, which was reflected on the blood ketone body ratio (BKBR)(the ratio of acetoacetate to beta-hydroxybutyrate in arterial blood). When the hepatic mitochondrial redox state was reduced after hepatectomy ($0.7>BKBR>=0.4$), hyperdynamic state was observed with increased cardic index, decreased systemic and pulmonary vascular resistance together with decreased oxygen consumption in spite of the increased oxygen availability. Therefore, oxygen extraction ratio and arterio-venous oxygen content difference were decreased. When the hepatic mitochondrial redox state was severely reduced ($0.4>BKBR$), hyperdynamic state was not observed any more, but the oxygen consumption decreased further. When the redox state in the liver mitochondria is reduced, oxidative metabolism such as Krebs cycle activity is inhibited. This study support the concept that the hepatic metabolic derangement due to reduced hepatic mitochondrial redox state may at least be a factor of decreased oxygen consumption and hyperdynamic condition.

156 NEUTROPHIL-MEDIATED CELL INJURY IN CULTURED RAT HEPATOCYTES. T. Nishihira*, T. Sato, K. Koizumi*, I.K. Berezesky* and B.F. Trump. Univ. of Maryland, Dept. of Pathology and MIEMSS, Baltimore, MD 21201.

Data obtained from studies using our septic rat model have suggested that the neutrophils seen in the liver sinusoids are closely related to hepatocellular injury associated with sepsis. We have studied hepatocellular injury mediated by neutrophils, especially mitochondrial (Mt) impairments, by assaying OCT release and ketone body ratio (AcAC/β-HOB) which links Mt redox. Hepatocytes (H) were obtained

by in situ collagenase perfusion and cultured for 24 hrs. Rat neutrophils (N) were obtained from the abdominal cavity 14 hrs after casein solution administration. Killed E. coli (E) was used for activation of neutrophils so that this study is relevant to the clinical setting. Treatments were done in MEM with normal rat serum plus supplements in the following 4 groups: H; H+E; H+N; H+E+N. Results suggest that neutrophils deteriorate Mt redox by some type of slow-acting mechanism(s) which seems to be different from any early effects on Mt membrane disintegrity presumably due to oxidative stress. (NIH GM 32084.)

	Ketone Body Ratio				% OCT Release		
	3 h	6 h	9 h	18 h	3 h	6 h	9 h
H	1.8±0.2	2.0±0.2	2.8±0.2	3.0±0.3	----	---	---
H+E	2.5±0.2	1.8±0.2	2.6±0.1	1.9±0.2*	118%	97%	97%
H+N	1.7±0.2	2.4±0.2	1.5±0.2*	1.1±0.1*	176%*	74%	79%
H+E+N	1.4±0.2	1.2±0.2*	1.0±0.1*	0.8±0.1*	206%*	99%	59%

M±SE, * p<0.05 comapred to H

M, * p<0.05 to H

157 CHANGES IN THE COMPLEMENT, FIBRINOLYSIS AND KALLIKREIN-KININ SYSTEM IN THE SEPTIC ELDERLY. H. Ogata, A. Shibusawa*. Dept. of Anaesthesia, Dokkyo Univ., Mibu. Tochigi, 321-02, Japan

Changes in the complement, fibrinolysis and kallikrein-kinin systems were investigated in septic patients suffering from cerebral vascular disturbances and immobilized for a prolonged period, and comparisons were made between those who died and the survivors in order to ascertain the cause of death. The subjects of the study were 19 patients. Of these, 15 died, the cause of death almost always being sepsis. Their clinical examinations: RBC, Hb, WBC, FDP, Fbg, PL, ESR, plasminogen, α_2MG, α_1AT, ATIII, C3, C4, CH50, prekallikrein, kininogen were analyzed retrospectively for the 16 weeks for fifteen deceased patients and for the 12 weeks for four survivors. The following conclusions were reached. 1) Hypoprotenemia, anemia and leukocytosis were markedly recognized in the deceased group. 2) There was no remarkable tendency of DIC, although the patients manifested septic shock and higher levels of FDP. 3) Activation of the plasmin, complement and kallikrein-kinin systems was observed in both groups, probably caused by endotoxin. 4) It was observed in the survivors that there were no remarkable decreases of RBC, Hb, serum protein, complement, (C3), (C4) or CH50 and no remarkable increase of WBC, FDP or ESR. These seemed to be effective indexes to determine the prognosis. From these, improvement of nutrition, prevention of infection especially from the urinary tract or decubitus, use of antiplasmic as well as antikallikrein agents and prevention of complement acitvation, especially invasion of endotoxin into the bloodstream were thought to be important.

158 CHANGES IN REGIONAL CEREBRAL BLOOD FLOW (rCBF) DURING ENDOTOXIN INDUCED SHOCK. A. Owunwanne*, A.A. Al-Sarraf*, J. Kuikka*, J.T. Christenson* (Spon: H. Shennib). Department of Surgery and Nuclear Medicine, Kuwait University, Kuwait.

Regional cerebral blood flow(rCBF)during endotoxin induced shock is unknown. The aim of this study was to investigate changes in the rCBF in sheep in vivo during endotoxic shock utilizing the first pass radionucleid technique. Eight sheep(30-45kg) were provoked to endotoxic shock by a slow i.v. injection of a lethal dose of E. Coli endotoxin 3mg/kg BW while monitoring carotid artery blood flow, ECG systemic arterial pressure and platelet count. The cerebral blood flow(CBF)over the left hemisphere was measured using an intraarterial isotope technique(first pass)prior to, 1,4,30 and 60 min after endotoxin inj. In vitro Tc-99m labelled red blood cells were used as tracer. Cerebral blood volume(CBV), cerebral transit time(CTT)and rCBF was calculated from the nuclear images. Blood pressure dropped 1 min after inj of endotoxin from 120±25 to 40±5mmHg followed by a short recovery at 5 min then gradually dropping. Carotid artery blood flow dropped 250ml/min to 60ml/min, 2 min after inj followed by a gradual increase and stabilization. CBV increased initially followed by gradual decrease(29% of initial volume at 1 hr). Left hemispheric blood flow prior to shock was 200±50ml/min. After endotoxin CBF dropped to 86±26ml/min(1 min), 110±53ml/min(4 min), 56±20ml/min(30 min) and 39±13ml/min(60 min after inj). The occipital rCBF showed the highest blood flow value prior to endotoxic shock whereas 60 min later in all brain regions rCBF was the same. This study shows a clear deterioration of CBF in endotoxic shock also that an autoregulatory mechanism retards the CBF decline at a time when blood pressure still is falling 4 min after induction of endotoxic shock.

159 ALBUMIN KINETICS IN PERITONITIS. M. Rowe*, H. Cheu*, and D. Lloyd* (Spon: T. Lobe). Children's Hospital of Pittsburgh and Univ. of Pittsburgh School of Medicine, Pittsburgh, PA 15213.

The massive loss of protein and fluid from the circulation is a major factor contributing to shock associated with peritonitis. The purpose of this study is to determine protein flux in peritonitis. Methods: 14 control and 14 peritonitis piglets were studied. Albumin kinetics between the blood, peritoneal cavity, and tissues was determined by sampling after injection of I-125 tagged albumin and Cr-51 tagged RBC's into the blood, and I-131 tagged albumin into the peritoneal cavity. Results: The disappearance of I-125 tagged albumin from the circulation was significantly greater in peritonitis: controls-6.9% at one hour, 36.4% at 6 hours; peritonitis-34.4% at one hour, 55.9% at 6 hours. A significantly greater amount of I-125 tagged albumin appeared in the peritoneal cavity of the peritonitis animals, 14% vs controls 4.1%. Albumin was rapidly absorbed from the peritoneal cavity of control animals; by 6 hours, only 28.3% of the I-131 albumin remained and 27% appeared in the blood. With peritonitis, absorption was inhibited; by 6 hours, 73.3% of the I-131 albumin remained in the peritoneal cavity and only 7.1% was detected in the blood. All comparisons had $p < .001$. Comment: The loss of albumin from the circulation in peritonitis appears to be the result of two mechanisms: 1) an increased "leak" of albumin into the peritoneal cavity and other tissues, 2) a marked reduction of reabsorption of albumin from the peritoneal cavity. Once albumin has "leaked" into the peritoneal cavity, it appears to be "trapped" and as a result, rapidly accumulates.

160 ALTERATIONS IN SERUM ALANINE CONCENTRATION INDUCED BY ENDOTOXIC SHOCK IN RABBITS AND ITS PROGNOSTIC VALUE. F.W. Schmahl, B. Bauer*, B. Metzler*. Dept. of Occupational and Social Medicine, University of Tuebingen, 7400 Tuebingen, Federal Republic of Germany.

Serum alanine levels have been shown to reflect the degree of catabolism in addition to various other metabolic parameters. Therefore serum alanine during endotoxic shock was analyzed in an animal model. Central venous blood was obtained from male mongrel rabbits (n=64, 6 months of age, 2-3 kg body weight immediately prior to and 2, 6 and 24 h after administration of endotoxin from E. Coli O 111 (50 µg/kg body weight over a 10 min period), as well as from age-matched controls (n=47). The serum concentrations of 16 amino acids were determined using gas chromatography. In contrast to the less pronounced changes in other amino acids a temporary, significant ($P < 0.0001$) increase of serum alanine above the initial level was observed 2 and 6 h after initiation of endotoxic shock. Infusion of a protease inhibitor (Gabexate mesilate, 1- and 2 µg/kg x min) during the 24 h period had no significant effect on the increase in alanine concentration. A significant ($P < 0.0001$) negative correlation between the survival rate of endotoxin-treated animals and the increase of alanine concentration 2 h after administration of endotoxin was observed. This finding is consistent with preliminary results from studies of our group in which changes in serum alanine and lactate concentrations in relation to the survival rate were compared. Our experiments indicate that alanine is a valuable prognostic parameter in this model of endotoxic shock.

161 GROUP B STREPTOCOCCAL(GBBS) NEWBORN SEPTIC SHOCK MODEL: ROLE OF PROSTAGLADINS(PGs) B. Short, M. Miller*, J. Pan*, The Children's Hospital National Medical, Washinton DC 20010.

Beta streptococcal sepsis remains the predominant organism in neonatal sepsis resulting in a high mortality(50-80%). As with gram negative sepsis, cyclooxygenase inhibition(Indomethacin, IND) has been shown to improve survival in rat septic models. This study was undertaken to study GBBS and the effect of PG inhibition on survival in a newborn septic model. 24-48 hr old newborn piglets were made septic by an IP injection of live GBBS organisms(10^{10}cfu). Hypotension was characteristically seen at 6 hrs post bacteria, therefore all therapies were given at that time. Group I: Control, 6cc saline IP; Group II: IND, 5mg/kg; Group III: OKY046 (Tx synth. inhibitor) 2mg/kg; Group IV: SQ29,548 (Tx receptor site inh.) 1mg/kg q 4hrs x 4. Results: Sepsis was characterized by hypotension, hemoconcentration, decrease in WBC count, decrease in platelet count, hypoglycemia in the first 2 hours of sepsis, and an average mortality of 70%. These parameters were not altered by any of the therapies except IND which increased survival from 30 to 81% at 72 hours post bact. Conclusions: (1) The newborn piglet is a good model for GBBS, (2) the cyclo.inh. consistently improves survival in this model, (3) the thromboxane inhibitors did not improve survival, (4) the mechanisms of action for the cyclooxygenation drugs remains unclear and may not be related to their inhibition of prostaglandins.

162 STUDIES OF THE HUMORAL IMMUNE RESPONSE IN A RAT INTRA-ABDOMINAL ABSCESS MODEL AGAINST E. COLI AND B. FRAGILIS ANTIGENS. Ben D. Tall*, Linda D. Lapierre*, Thomas C. Vary, John H. Siegel, and J. Glenn Morris. Center Vaccine Development and MIEMSS:Depts. of Surgery, Physiology, UMAB, Baltimore, MD 21201.

A rat intra-abdominal abscess (IAA) model was used to investigate the humoral immune response against two bacterial pathogens often isolated from IAA in man, E. coli (EC) and B. fragilis (BF). Intra-abdominal abscesses were made with a fecal-agar pellet (1.5 ml vol.) containing known concentrations of bacteria. SDS-PAGE was performed on whole cell lysates of 2 strains of EC, with different virulence properties, Stu-1(EC1, LD_{50} $4X10^2$cfu), and Ming (EC2, LD_{50} < 10^1cfu) and BF. 46, 49 and 44 peptides were identified, respectively. Immunoblot analysis was performed using rabbit hyperimmune sera, nonimmune rat plasma (A), plasma from rats inoculated with sterile fecal pellets (B), or with EC(EC1 or EC2)/BF infected pellets (C). Anti-EC1 rabbit sera identified ~ 48 EC1 peptides. Anti-EC2 rabbit sera identified ~ 55 EC2 peptides. Anti-BF rabbit antisera recognized ~ 47 BF peptides. Immunoblot analysis of EC and BF peptides with group A plasma identified 3 EC, but no BF peptides. Group B plasma recognized an additional EC peptide and one BF peptide. Group C-EC1 plasma recognized 24 major EC1 peptides. While group C-EC2 plasma recognized 23 EC2 peptides many of which were the same molecular weight as the EC1 peptides, while others were not. In contrast, group C plasma recognized 14 BF peptides. Our data shows in a rat IAA model an immune response is mounted towards a variety of EC and BF peptides, and that the EC peptides identified may be important virulence and/or protective antigens.

163 THE EFFECT OF CIPROFLOXACIN, METRONIDAZOL, AND/OR ENDOTOXIN ON EXPERIMENTALLY INDUCED GUT-DERIVED SEPTICEMIA. Renate Urbaschek*, K.-P. Becker*, Petra Unold*, F. Gutzler*[2] and B. Urbaschek. Dept. of Immunol. & Serol. Klinikum Mannheim, University of Heidelberg; [2] Dept. of Clinical Pharmacology, University of Heidelberg, West Germany.

Severe, gut-derived septicemia was induced by cecal ligation and puncture in anesthezised NMRI mice. This experimental model was used to study the effect of metronidazol (ME 10 mg/kg) and/or ciprofloxacin (CI 10 mg/kg) - a new quinoline carboxylic acid derivative (BAYER, Wuppertal) - on the mortality rate in groups of 15 mice each. Starting at two hours after surgery the antibiotics were given alternately s.c. and i.v. every 12 hours for 7 days. In earlier studies we observed that 24 hour pretreatment with 1 µg of endotoxin, ET, (TCA extract of E. coli 055) resulted in a reduction of lethality, so that a combination of ET pretreatment and CI treatment was used in 13 mice. The lethality rates at 2 days/14 days were: controls 80%/94%; ME 67%/87%; CI 20%/60; ME+CI 27%/40%; ET 34%/48%; ET+CI 15%/23%. Thus, the most effective treatment was the combination of ET+CI. The number of both anaerobic and aerobic bacteria isolated at 14 days from liver, and spleen from survivors was lower after combined treatment: ME+CI, and ET+CI. In the latter groups no bacteria were found in blood whereas in the blood of survivors treated with ME or CI alone bacteria were present. - A comparison of the levels of CI in plasma, liver, spleen, and kidney at 2 h after the 2nd injection revealed that the concentrations were significantly higher in septicemic versus control mice, indicating that during the state of shock antibiotics accumulate to a much higher degree than expected from clearance studies in healthy animals.

164 **THE ROLE OF COMPLEMENT IN GLUCAN-INDUCED PROTECTION AGAINST GRAM-NEGATIVE SEPTIC SHOCK.** D. WILLIAMS*, E. SHERWOOD*, I. BROWDER*, R. MCNAMEE* AND E. JONES* (Spon. James A. Cook). DEPARTMENTS OF PHYSIOLOGY AND SURGERY, TULANE UNIVERSITY SCHOOL OF MEDICINE, NEW ORLEANS, LA 70112.

Previous studies from our laboratory have shown that glucan will significantly enhance survival, decrease bacteremia, maintain reticuloendothelial function and reduce histopathology in a murine model of gram-negative septic shock (Williams et al., Surgery 93:3, 448-454, 1983). The present study was undertaken to evaluate the role of complement in glucan-enhanced protection against septic shock. AKR/J mice, which are congenitally C5 deficient, and ICR/HSD mice that were rendered complement deficient by treatment with purified cobra venom factor (CVF), were injected IP with glucan (1 mg/mouse) on days 5 and 3 prior to IP challenge with 1 x 10^8 E.coli. Survival data indicated that glucan ($p<0.05$) increased survival (100% vs. 0%) in both C5 deficient and complement depleted mice. Glucan prophylaxis resulted in a neutrophilic leukocytosis 8 hrs. following E. coli challenge. However, glucan did not alter bone marrow proliferation or splenocyte mitogenesis. Serum from glucan-treated animals showed a 40% ($p<0.05$) increase in bactericidal activity for E. coli at 60 min. The increased bactericidal activity of glucan serum was lost following inacti-

vation of complement. We conclude that: 1) glucan's protective effect on survival is not dependent on complement; 2) complement is not required for glucan-induced neutrophilic leukocytosis; 3) glucan does not enhance bone marrow proliferation or splenocyte mitogenesis in complement deficient mice and 4) the increased serum bactericidal activity against E. coli, observed in glucan-treated mice, is complement dependent.

165 STEROIDAL AND NON STEROIDAL ANTI-INFLAMMATORY AGENTS HAVE OPPOSITE EFFECTS ON GLUCOSE OXIDATION BY THE NEONATAL ENDOTOXIC LIVER. Linda Witek-Janusek and Cheryl Pacini*. Depts. Physiology and Maternal Child Health Nursing, Loyola University, Maywood, IL 60153

Neonatal endotoxemia results in glucose dyshomeostasis that is associated with increased liver glucose oxidation (GO). This study compared the effects of methylprednisolone (MP), indomethacin (IND) and ibuprofen (IBU) on GO by the neonatal endotoxic liver. Ten day old fed rats were injected i.p. with either 40 mg/kg MP, 5 mg/kg IND, 25 mg/kg IBU or saline (SAL) 30 min prior to 0.1mg/kg i.p. S. enteritidis endotoxin (ETX) or SAL. Liver slices (0.5mm) obtained at 3 hr post ETX were placed in metabolic flasks containing Krebs-Ringer bicarbonate with 0.5 μCi U-[^{14}C]-D-glucose and 5.55 mM D-glucose. Evolved $^{14}CO_2$ was collected at 2 hr. Results in DPM/gm/2hr x10^3 are below:

Pretreat. →	SAL	(N)	MP	(N)	IND	(N)	IBU	(N)
SAL	326±29[a]	(18)	248±45	(4)	400±24	(11)	517±50[b]	(7)
EXT	521±35	(21)	268±47[c]	(6)	747±48[c]	(10)	734±25[c]	(7)

Values=$\bar{X}$±SEM; [b]$p<.05$ compared to SAL+SAL; [c]$p<.05$ compared to SAL+ETX

MP significantly decreased GO in the ETX liver; while, IND and IBU appear to synergize with ETX and hence further increase GO by the neonatal liver. IND and IBU did not change ETX 24 hr mortality (80%) but MP provided 100% survival. Thus, the protective versus non-protective effects of these agents in the endotoxic neonate may be related to their actions on liver glucose utilization (Supp. by HL 31163).

166 EVALUATION OF IMMUNOREACTIVE INSULIN (IRI) SECRETION FROM ISOLATED PANCREATIC ISLETS OF ENDOTOXIN-(E) OR INTERLEUKIN 1-(IL-1) TREATED RATS. M.R. Yelich, D.M. Umporowicz*, E.A. McCulla* and J.P. Filkins. Dept. Physiol., Loyola Univ. of Chgo., Stritch Sch. of Med., Maywood, IL 60153.

E in vivo induces an IRI hypersecretory state in the perfused rat pancreas. IL-1, a monokine from E-stimulated macrophages, also induces IRI hypersecretion from the perfused pancreas and may mediate the effects of E on IRI secretion (Fed. Proc. 46:1987). This study evaluated glucose-induced IRI secretion in islets isolated from pancreases of rats treated with either E or IL-1. E (S. enteritidis, 16.7 mg/kg) or IL-1 (Collaborative Research, Inc., human, 250 U/kg) was administered iv to Sprague-Dawley rats at 3 hr or 45 min, respectively, prior to isolation of islets by collagenase digestion. 5 islets were incubated for 1 hr in 5.0 mls of medium containing 300 mg/dl glucose. The data are shown below as mean total IRI (μU)/5ml/hr ± SEM (n) = # of duplicate experiments.

IV TREATMENT	TOTAL IRI/5ML/HR	% Diff. vs Control	(P-VALUE)
CONTROL	528 ± 40 (4)	--	--
ENDOTOXIN	750 ± 78 (4)	+42%	< 0.05
INTERLEUKIN-1	507 ± 44 (4)	- 4%	NS

Thus, islets from endotoxic rats demonstrated the IRI hypersecretory state, while islets from IL-1 treated rats failed to demonstrate altered IRI secretion. Since either E or IL-1 induce IRI hypersecretion in the intact perfused pancreas, these results suggest that E-induced IRI hypersecretion may be mediated by IL-1 signaling and additional mechanisms. (Support: NIH Grants AM 36044, HL 31163)

167 QUANTITATIVE CORRELATION OF ENDOTOXIN IN BLOOD AND ASCITES OF PATIENTS WITH SEVERE PERITONITIS TO ORGAN FAILURE AND OUTCOME. D.Berger*, W.Oettinger and H.G.Beger. Dept. of General Surgery, Univ. Ulm, Steinhoevelstr.9, 7900 Ulm, FRG.

Endotoxin (ET) is believed to be the primary mediator of gram-negative sepsis. However, its determination and subsequent correlation to clinical patterns is still controversial. Therefore we analysed 50 well stratified patients with a defined state of severe peritonitis (intestinal perforation) using a reassessed endotoxin test. Data were followed-up three times daily for 3-35 days and correlated to vital organ failure and final outcome leading to the following results:

	vital organ failure	mortality
1. Endotoxin >100 EU/ml in >5 samples	9/9 = 100%	7/9 = 78%
2. Only E. coli in ascites	18/25 = 72%	5/25 = 20%
3. Mixed cultures in ascites (Klebs.,Enterob.)	8/18 = 44%	2/18 = 11%
4. Gram-positive ascitic culture (no significant endotoxemia)	5/7 = 71%	2/7 = 28%

(EU = endotoxin units)

Data suggest that ET levels >100 EU/ml might serve as predictors of vital organ failure and high mortality in patients with severe peritonitis. Monocultures of E. coli in ascites seem to be the most productive sources of ET. It is seen as the result of the specificity of our test that in patients with exclusive gram-positive growth - regardless of ensuing organ failure - no significant ET concentrations are detectable.

168 MURINE MONOCLONAL ANTIBODY TO LIPOPOLYSACCHARIDE (LPS) INHIBITS KUPFFER CELL ACTIVATION BY ENDOTOXIN IN VITRO. T. Billiar*, M. West*, B. Hyland*, R. Simmons*, D. Dunn* (Spon: F. Cerra) Univ. Minnesota, Minneapolis, MN 55455.

Activation of macrophages by circulating endotoxin contributes to septic shock acutely and may mediate many of the long-term sequelae of sepsis. Inhibition or reversal of the effects of LPS on macrophages might prevent some lethal septic complications. Using an in vitro rat hepatocyte (HC):Kupffer cell (KC) co-culture system we have previously shown that LPS activated KC induce a significant decrease in HC protein synthesis (as shown by 3H-leucine incorporation) when compared to HC alone, HC with LPS, or HC with KC (no LPS). To determine whether this effect could be inhibited, murine monoclonal antibody (McAb) to LPS (E.coli 0111:B4) was added to cell cultures after the addition of LPS. The addition of McAb 100ug/ml immediately after LPS effectively prevented the decrease in 3H-leucine incorporation seen with LPS alone. These data suggest that LPS bound by antibody may be incapable of inducing KC/macrophage activation and that anti-endotoxin antibodies might be useful in preventing macrophage induced complications in sepsis.

PROTEIN SYNTHESIS
(% HC* cultured alone + SE)

	HC	HC + KC
Media	100 ± 3.7*	120 ± 4.4†
LPS 1 ug/ml	104 ± 4.7	75 ± 2.3†§
McAb	107 ± 1.0	105 ± 4.6
LPS 1ug/ml+McAb	110 ± 5.4	106 ± 2.9§

(†,§ $p<0.001$)

169 METABOLIC AND HISTOLOGIC ALTERATIONS IN TNF-INDUCED SHOCK. M.J.Ciancio*, S.B.Jones, N.A.Sacco*, J.P.Filkins. Loyola Univ. Medical Center, Maywood, IL 60153.

Tumor necrosis factorα/cachectin (TNF) may be a major mediator of the endotoxic syndrome. This study evaluated the shock-like metabolic and histologic changes induced by recombinant TNF(Genentech) in fed conscious male Holtzman rats(358±13g). Venous and arterial cannulas were surgically implanted on the morning of experimentation. Rats were then given an i.v. bolus injection of either saline(S; n=5) or TNF(1 ug/g; n=5). Arterial samples were taken at 0, 30, 60, 90, 180, and 360 min. Heart rate(HR) and mean blood pressure(BP) were monitored. Tissue was taken, formalin fixed, paraffin embedded, sectioned(6um) and H+E stained for light microscopy. In accord with previous results (Fed. Proc. 46: 1987), TNF induced a shock-like state. HR progressively increased from a control value of 413±13 to 542±33bpm, whereas BP remained steady until time of death. Plasma glucose levels increased from a control value of 158±4 to 195±14mg/dl by 60 min. Plasma lactate levels progressively increased from a control value of 0.78±0.08 to 2.3±0.6mM. Agonal plasma samples demonstrated a profound hypoglycemia and hyperlactacidemia. Microscopic examination of lung, liver, and kidney revealed erythrocyte engorged vasculature and profuse hemorrhagic foci. Polymorphonuclear cell infiltrates were seen in hepatic sinusoids and alveolar walls. Lethality at 6h was 5 out of 6 in fasted versus 2 out of 5 in fed rats. S animals demonstrated no metabolic or histopathologic alterations. Induction of a shock-like state by TNF supports the concept that monokines released from activated macrophages may mediate the endotoxic syndrome. (Support: NIH grant HL31163).

170 RENAL RESPONSE TO ENDOTOXIN (LPS) IN SHEEP. H. Lubbesmeyer*, L. Traber*, R. Kimura*, D. Herndon, D. Traber. U TX Med Br and Shriners Brns Inst, Galveston, TX, 77550.

Despite their frequent coexistence the nature of the relationship between sepsis and renal impairment remains obscure. METHODS: Sheep (N=5) were prepared for chronic study by placing catheters in the cardiovascular system and a catheter in the urinary bladder. After a 12 hr equilibration period during which maintenance fluid (2cc/Kg/h of Ringers lactate) was given, control data were obtained in the unanesthetized state and 1.5 us/Kg of LPS administered.

	CONTROL	2 HOURS	4 HOURS	6 HOURS	12 HOURS
Cardiac Index ($l/h/m^2$)	6.9±0.7	7.0±0.5	5.4±0.4*	6.1±0.4	8.6±0.6*
Urine Output (ml/min)	1.6±0.3	2.4±0.6	3.7±0.7	5.3±1.8*	1.3±0.6
Filtered Na+ Excretion Fraction (%)	1.1±0.4	1.1±0.5	3.4±1.4*	4.5±1.1*	0.3±0.1
Osmolar Clearance (ml/min)	2.5±0.6	4.3±0.9	5.2±1.3*	6.1±0.9*	2.1±0.5

MEAN±Standard Error *=p<0.05 (Dunnetts test after ANOVA)

Despite the early drop in cardiac index (CI) there was a marked increased in urine output. At 6 hrs post LPS, CI had reached baseline level and urine output was elevated 230% above baseline with an unchanged creatinine clearance. This is in agreement with the clinical evidence that early renal dysfunction in sepsis is characterized by a loss of urinary concentrating ability indicating a possible redistribution of renal blood flow, a loss of medullary concentration gradient and a subsequent inappropriate diuresis. The significant increase in sodium excretion fraction is an indicator of possible acute tubular necrosis. Therefore, endotoxemia produces a severe renal impairment similiar to the human sepsis.

171 EVIDENCE FOR LACK OF IMPORTANCE OF OXYGEN FREE RADICALS IN E. COLI ENDOTOXICOSIS IN DOGS. M.J. Novotny*, M.H. Laughlin*, V.K. Ganjam*, and H.R. Adams. Dept. of Veterinary Biomedical Sciences. Univ. of Missouri, Columbia, MO 65211.

Reactive oxygen species have been proposed as pathophysiologic factors operative during gram-negative endotoxin shock. To test this hypothesis, we examined the influence of a battery of mechanistically different oxygen free radical scavenging agents on the systemic toxicity of E. coli endotoxin (ET) in Beagle dogs. Pentobarbital-anesthetized dogs were: (1) instrumented for repeated sampling of cardiorespiratory, hematologic, plasma PGI_2/TxA_2 (radioimmunoassay), and tissue blood flow (radiolabeled 15 μm microspheres) indices; (2) injected IV with saline (time-matched controls; n=6) or ET (1.5 mg/kg; n=20); and (3) studied for 4 hrs. ET dogs also received either IV saline (shock controls; n=6) or IV treatment with allopurinol (50 mg/kg; n=3), deferoxamine (30 mg/kg; n=5), or triple therapy (n=6) with a combination of allopurinol, superoxide dismutase (5 mg/kg), and catalase (5 mg/kg). Measured variables in sham-shock controls were constant during the study; whereas, ET dogs developed: (1) persistent reductions in blood pressure (>45%), left ventricular systolic pressure (>43%), dP/dt (>41%), cardiac ouput (>50%), and blood flow in all sampled tissues except diaphragm; (2) transient tachypnea, bradycardia, and arterial acidosis; (3) neutropenia and hemoconcentration; and (4) increases in plasma 6-keto-$PGF_{1\alpha}$ (>600%) and TxB_2 (>100%). None of the free radical scavenging protocols significantly improved variables during ET shock ($p>0.05$, ANOVA), suggesting that superoxide anion, hydrogen peroxide, and hydroxyl radical lack primary importance during the developmental phase of E. coli endotoxicosis.

172 EXPERIMENTAL SEPTIC SHOCK: EFFECT ON SURVIVAL WITH VARIOUS TREATMENT REGIMENS. J. Ottosson*, I. Dawidson, J. Reisch*. Univ. Texas Health Sci. Ctr.,Dallas TX 75235.

This study examines the effect on survival of an antibiotic drug (trimethoprim, 50 mg/kg + sulfamethoxazole, 250 mg/kg) (TS), Ringer's lactate (RL), 3% colloid solution (COL) infusions, and dexamethasone (DM), given alone and in combinations. Therapy was initiated 5.5 h after inducing sepsis by intraperitoneal injection of 5×10^8 live E. coli bacteria. COL and RL were infused during 4 h in volumes of 9 and 27 ml/100 g body weight, respectively, to maintain preshock blood volumes. DM was given twice, at 5.5 and 8.5 h, in a total dose of 8 mg/kg. Survival was recorded hourly for 24 h and at 7 days.

Treatment group	Survival time (h) Mean ± SD	24-hour survival No./total	%	7-day survival No./total	%
C	9.6 ± 1.7	0/52	0	0/52	0
TS	10.9 ± 3.1	0/52	0	0/52	0
TS + DM	12.3 ± 3.2*	31/52	60***	13/52	25**
TS + RL	14.5 ± 4.5*	19/50	38***	6/50	12**
TS + COL	15.5 ± 4.0*	42/82	51***	18/82	22**
TS + RL + DM	12.6 ± 4.4*	41/52	79***	5/52	10**
TS + COL + DM	--- *	51/52	98***	22/52	42**

*p<0.05; **p<0.01; ***p<0.001 (in relation to groups C and TS)

In this septic shock, the best treatment was the combination of antibiotics, 3% colloid infusion and dexamethasone (TS + COL + DM), resulting in greater 24-h ($p<0.001$) and 7-day ($p<0.05$) survival rates than any other treatment tested.

173 SUPPRESSION OF TISSUE LIPOPROTEIN LIPASE (LPL) ACTIVITY BY IN VIVO INFUSION OF CONDITIONED MEDIUM FROM ENDOTOXIN-TREATED RAW 264.7 CELLS. G.J. Bagby, C.B. Corll*, R.R. Martinez*, L.A. Wilson*, and J.J. Thompson*. Louisiana State Univ. Med. Ctr, New Orleans, LA 70112.

Endotoxin (ET)-induced suppression of adipose tissue LPL activity is mediated by macrophage secretory proteins collectively termed monokines; however, decreased LPL activity also occurs in other tissues after ET administration but the role of monokines in this suppression has not been demonstrated. The present study was initiated to determine if infusion of monokine-containing conditioned medium from ET-treated (1ug/ml) RAW-264.7 cells (RAW-CM) would alter tissue LPL activity in ET-tolerant rats. Catheterized rats were made tolerant to ET by 5 successive daily injections of ET. ET (100 g/100g) administration to nontolerant rats decreased total heart, heparin-releasable heart and skeletal muscle LPL activity, but did not alter activity in tissues of ET-tolerant rats. A 3 hr i.v. infusion of a 100-fold concentrate of RAW-CM (1 ml prime, 3 ml/hr infusion) into ET-tolerant rats resulted in 66% lethality during the first 5 hrs. Suppression of heart LPL activity occurred in ET-tolerant rats given 10-100 fold concentrates of RAW-CM. The greatest decrease was observed in heparin-releasable LPL activity in isolated perfused hearts (less than 10% of control). Soleus muscle LPL activity tended to be decreased but adipose tissue activity was unaffected by RAW-CM treatment. In conclusion, infusion of conditioned medium from ET-treated RAW 264.7 cells into ET-tolerant rats suppresses tissue LPLA in a manner similar to that observed in nontolerant rats given endotoxin. (Supported by GM 32654).

174 RIBOSE AFFECTS MORTALITY AFTER REVERSIBLE HEPATIC ANOXIA. Paul Bankey*, Herbert Ward*, Steven Eyer*, William Becker*, Frank Konstantinides*, Frank Cerra. Dept. of Surgery, St. Paul Ramsey Medical Center and University of Minnesota, Box 42 Mayo, Minneapolis, MN 55455.

Ribose improves cardiac performance and ATP recovery after anoxia. To test if ribose might improve recovery from hepatic anoxia, 18 dogs underwent 90 min of reversable, normothermic, anoxia with 48 hours of awake reperfusion. A portacaval side-to-side shunt was done prior to anoxia to prevent bowel stasis during anoxia. IV fluid was given at 100 ml/kg/day. Group A(6) received saline; Group B(6) Ribose (100 mg/kg/hr) and Group C(6) Ribose and Glucose (each 100 mg/kg/hr). During anoxia plasma amino acid clearance (PAAC) and hepatic ATP fell to 10% of baseline ($P < .001$) and serum lactate (Lac) rose to 100% of baseline ($P < .01$).

% Change from Baseline at 24 Hours Reperfusion			* P<.03 Group C to A & B or Group B to A & C
	Group A	Group B	Group C	
SGOT	+27500±1000	+11800±500*	+250±50*	**P<.05
OTC	+ 500± 50	+ 1500± 40*	+ 50± 5*	~ P<.05 Group B & C to A
PAAC	- 75± 20	+ 400± 30*	+100±15*	+ means increased, - means decreased
ATP	- 40± 10	- 50± 15	+ 20± 5*	
% Mortality	**25	**50	**0	OTC=serum ornithine transcarbamylase

The determinants of survival were PAAC, OTC, ATP and carbohydrate type (r^2.88, P<.001). Ribose is detrimental to hepatic function and survival after anoxia, possibly by potentiation of mitochondrial injury.

175 GLUCOSE NET PRODUCTION(GNP) IN THE ISOLATED NEWBORN RAT LIVER WITH ENDOTOXICOSIS. M. Goto, W.P. Zeller,* R.M. Hurley*, and J.P. Filkins. Dept of Pediatrics and Physiology, Loyola University,Stritch Schl of Medicine, Maywood, IL 60153(Support HL-31163)

Glucose dyshomeostasis as manifested in profound hypoglycemia,has been well documented in both adult and newborn endotoxicosis. However,the pathophysiological mechanisms in newborns are not clearly understood. Since the liver is a key organ of neo natal glucose regulation,GNP was measured in the isolated perfused liver from newborn rats. 10 day old Sprague-Dawley rats were divided into 4 groups as follows: Group 1(n=7)was used in the fed state. Group 2 (n=6)received 0.1 mg/kg of S.enteritidis endotoxin(LPS) ip in the fed state. Group 3(n=6)was fasted for 4 hours. Group 4 (n=7)received LPS after a 4 hour fast. Group 2 and Group 4 were utilized 2 hrs after

LPS. The isolated liver was perfused via the portal vein in a recirculating perfusion apparatus using Krebs-Ringer-Bicarbonate solution which was gassed with 95%02 and 5%CO2 at 37°C. Glucose was measured in the perfusate at 5 min.intervals for 75 mins. GNP(mg/g liver) was calculated. (Mean ± SE)

	25 min	50 min	75 min	
Group 1	3.44±0.87	3.91±0.96	3.47±0.97	
Group 2	2.38±0.78	3.13±1.30	2.87±1.48	(*p<0.01
Group 3	2.53±0.76	3.01±0.40	2.26±1.23	Group 3 vs Group 4)
Group 4	0.62±0.52*	0.91±0.88*	0.67±0.67*	

GNP in Group 2 and 3 tend to be decreased. GNP in Group 4 is markedly suppressed. Conclusion: In vitro GNP is a useful method to investigate the liver's role in gluco-regulation of newborn endotoxicosis.Decreased GNP may explain the severe hypoglycemia.

176 ATTENUATION OF ENDOTOXIN-INDUCED INCREASE IN GLUCOSE METABOLISM BY PLATELET-ACTIVATING FACTOR (PAF) ANTAGONIST. CH Lang, C Dobrescu*, DM Hargrove*, GJ Bagby and JJ Spitzer. Dept. Physiology, LSU Med. Ctr., New Orleans, LA 70112.

PAF has been proposed as a putative mediator of the early hemodynamic events of endotoxemia. The aim of the present study was to determine the potential importance of PAF in producing the alterations in glucose metabolism after endotoxin (ET). Chronically catheterized conscious male rats were treated with SRI 63-441, a specific PAF receptor antagonist, or saline prior to E. coli ET (100ug/100g BW, LD_{10}). Glucose kinetics, assessed by constant iv infusion of [6-^{3}H] glucose, were determined throughout the 4 hr experimental protocol. Rats treated with ET exhibited a transient 30-35% reduction in mean arterial blood pressure (MABP); SRI 63-441 partially attenuated this hypotensive effect and MABP was only reduced 14-18%. In saline-treated rats, ET increased plasma glucose and lactate concentrations, as well as the rate of glucose appearance (Ra). SRI 63-441 reduced the ET-induced hyperglycemia by 60-80%, tended to prevent hyperlactacidemia, and attenuated the elevation in glucose Ra by 55%. A similar degree of hyperglucagonemia was observed after ET in both groups and plasma insulin levels were also not different. The markedly increased plasma catecholamine levels were lower (30-70%) in ET rats treated with SRI 63-441. These results suggest that the enhanced production of PAF following ET may be in part responsible for the early hemodynamic and metabolic changes. However, whether the glucose dyshomeostasis is a direct effect of PAF or secondary to the hemodynamic changes remains to be elucidated. (Supported by NIH GM 32654).

177 IN VIVO HEPATIC INSULIN RESISTANCE DURING ENDOTOXIC SHOCK. M.P. McLane* and R.M. Raymond. Depts. of Surgery and Physiology, Loyola University Medical Center, Maywood, IL 60153 and the VA Hospital, Hines, IL 60141.

To study the effects of shock on hepatic insulin responsiveness, 11 healthy mongrel dogs were anesthetized. Catheters were inserted into the portal and hepatic veins and hepatic artery. Blood flow was measured with electromagnetic flow probes. Net hepatic balance of substrates was determined using the Fick technique. Dogs were divided into two groups: after baseline measurements, CONTROL (n=4) dogs had a hyperinsulinemic (4 U/min i.v.), euglycemic clamp (INS) established in the presence or absence of of adenosine (10^{-5} mol/min) infusion (ADO). Following baseline measurements, SHOCK (N=7) was induced by the i.v. injection of 1 mg/kg S. typhimurium endotoxin.

	CONTROL			SHOCK			
	BASAL	INS	INS+ADO	BASAL	SHOCK	INS	INS+ADO
Glucose Uptake (mg/kg-min)	-4.5±0.7	4.4±4.6	-1.8±2.2	-3.6±0.9	-1.0±1.1	1.3±0.7	1.9±0.9
Lactate Uptake (μmol/kg-min)	-13.6±14.1	7.2±8.2	-11.1±12.8	-10.4±5.7	-8.4±8.0	-2.6±5.4	1.9±1.0
Oxygen Uptake (ml/min)	38±7	67±35	10±20	44±10	43±18	42±16	46±18

The results suggest that 1) hyperinsulinemia while euglycemic inhibits net hepatic glucose and lactate output less in SHOCK compared to CONTROL dogs and 2) adenosine infusion blocks the insulin-induced inhibition of hepatic glucose and lactate output in CONTROL but not SHOCK dogs. Thus, the in vivo hepatic insulin resistance observed during shock may be mediated by adenosine and may effect the glucose transport system while the post-transport metabolism is still insulin-responsive. (Supported by NIH grant HL-31163 and the VA).

178 **CONTRIBUTION OF DIFFERENT ORGANS TO INCREASED GLUCOSE UTILIZATION AFTER ENDOTOXIN ADMINISTRATION.** **K. Mészáros*, C.H. Lang, G.J. Bagby and J.J. Spitzer. Department of Physiology, LSU Medical Center, New Orleans, LA 70112.**

Glucose utilization rate of individual organs of conscious rats was determined 3h after treatment with 100 ug/100 g of E. coli endotoxin (ET) by the iv 2-deoxy-

glucose (2DG) tracer technique. Glucose utilization was calculated from: a) the accumulation of non-metabolizable, phosphorylated derivatives of 2DG in tissues; b) disappearance of 2DG from the blood; and c) discrimination against 2DG in pathways of glucose metabolism (as reflected by the lumped constant determined in isolated tissues). ET increased glucose utilization in the liver (4.8 fold), spleen and skin (2.9 fold), lung (2.4 fold), intestine and kidney (2.1 fold), and in different skeletal muscles (1.5 to 2 fold), as compared to time-matched controls. No significant change occurred in brain and testis (protected by tissue-blood barriers), and in whole blood. The sum of glucose utilization by these organs in control and ET-treated rats (12.7 and 25.4 umole/min/rat, respectively) compared well with whole-body glucose disappearance rate determined by constant infusion of [6-^{3}H]glucose (11.8 and 19.7 umole/min/rat). The largest consumers under control conditions were the skeletal muscle mass (30%), intestine (26%) and skin (23%), which also accounted for more than 80% of the increase in glucose utilization after ET. The marked effect of ET on tissues rich in mononuclear phagocytes (e.g. liver, spleen) is likely to reflect the elevated metabolic demands of the activated defense mechanisms. (Supported by NIH GM 32654.)

179 ADENOSINE MEDIATION OF SKELETAL MUSCLE INSULIN RESISTANCE DURING CHRONIC HYPERDYNAMIC SEPSIS IN THE DOG. R.M. Raymond, R. Roy* and N. King*. Depts of Surgery and Physiology, Loyola University Medical Center, Maywood, IL 60153 and the VA Hospital, IL 60141.

Adenosine has been reported to directly induce skeletal muscle insulin resistance in normal, healthy animals and was implicated as a mediator during several endocrinopathies. The present study was undertaken to test the hypothesis that skeletal muscle insulin resistance is induced by adenosine, during chronic hyperdynamic sepsis in the dog. Large mongrel dogs (n=10) of either sex weighing 20-25 kg were made septic by the implantation of a human fecal innoculated gauze sponge, amid the intestines, through a midline laporotomy. On the third day of sepsis animals were anesthetized, intubated and ventilated artifically. The innervated, constantly perfused gracilis muscle preparation was used as the test organ. adenosine (ADO; 10^{-8} mol/min) was infused with insulin (Ins; 500 mU/min) in control (n=4) animals and adenosine deaminase (ADA; 200 mU/min) was infused with insulin during sepsis (n=6).

	Control			Sepsis		
	Basal	*Ins.*	*Ins+ADO*	Basal	Ins.	Ins.+ADO
Glucose uptake (mg/min/100g	.32	1.16*	.44+	.21	.31	.88+

(*=p<0.05 re: Basal; +=p<0.05 re: corresponding Ins)

These data demonstrate that 1) adenosine induces insulin resistance in control animals; 2) sepsis results in skeletal muscle insulin unresponsiveness and 3) ADA can reverse the insulin resistance during sepsis. These data support the hypothesis that skeletal muscle insulin resistance is mediated by adenosine during chronic hyperdynamic sepsis. (Supported by NIH grant HL-31163 and the VA)

180 EFFECT OF BUTHIONINE SULFOXIMINE PRETREATMENT ON RAT RENAL GLUTATHIONE CONTENT AND RECOVERY FROM RENAL ISCHEMIA. Russell Scaduto, Jr.*, Lee W. Grotyohann* and Louis F. Martin. The Departments of Surgery and Physiology, The Milton S. Hershey Medical Center, The Pennsylvania State University, P. O. Box 850, Hershey, PA 17033.

The metabolism of glutathione (GSH) serves to protect cells against damage caused by oxidative stress. GSH is a scavenger of free radicals, and an important component in the recycling of α-tocopherol and the glutathione peroxidase-mediated reduction of hydroperoxides. Since ischemia and blood reflow to ischemic tissue causes an increase in tissue free radical generation and lipid peroxidation, we examined the role of GSH in renal ischemia. Control rats and rats pretreated with L-buthionine sulfoximine (BSO) underwent either 35 minutes of renal artery occlusion or sham surgery following contralateral nephrectomy. BSO pretreatment lowered total renal GSH to 20% and cortex mitochondrial GSH to 50% of control values through inhibition of GSH synthesis. Following release of the occlusion, the kidney was prepared for clearance studies after which the kidney was either freeze clamped for metabolite determinations or removed for isolation of cortex mitochondria. Total renal GSH was 61% and cortical mitochondrial GSH content was 62% of control values 90 minutes following release of the renal artery occlusion. These changes were associated with a marked decrease in the renal ATP and total adenine nucleotide content. Ischemia did not affect renal GSH in BSO pretreated rats. Furthermore, BSO pretreatment did not alter the decrease in adenine nucleotides or GFR or the increase in LDH excretion caused by ischemia. The data suggest that a lowered renal GSH content does not affect recovery from renal ischemia.

181 DICHLOROACETATE (DCA) REVERSES SEPSIS-INDUCED INCREASES IN GLUCOSE KINETICS. John J. Spitzer, Gregory J. Bagby, Howard L. Blakesley* and Charles H. Lang. Dept. Physiology, LSU Med. Ctr., New Orleans, LA 70112.

Recent studies indicate that pyruvate dehydrogenase (PDH) activity in skeletal muscle is reduced during sepsis which may contribute to the altered glucose kinetics seen in this condition. The aim of the present study was to determine if DCA, a known stimulator of PDH, could reverse the increase in glucose kinetics observed during infection. Hypermetabolic sepsis was produced in chronically catheterized rats by repeated subcutaneous injections of *E. coli*. Glucose kinetics, assessed by constant iv infusion of [6-^{3}H and U-^{14}C] glucose, were determined in septic and nonseptic rats prior to and after an iv injection of DCA (30 mg/100 g BW). Sepsis produced hyperthermeia(+1.6°C) and increased rates of glucose appearance (Ra; 95%), recycling (318%), metabolic clearance (MCR; 114%) and elevated plasma lactate levels (295%) compared to nonseptic controls. After injection of septic animals with DCA, glucose levels were reduced by 45% at the end of the 4 hr protocol. DCA decreased the sepsis-induced hyperlactacidemia to values not different from controls over the final 2 hrs. Treatment of septic rats with DCA reduced the elevated glucose Ra and recycling within 30 min. Glucose Ra continued to fall and was not different from nonseptic rats at 4 hrs; recycling, although reduced, was still elevated by 50%. DCA did not alter the sepsis-induced increase in MCR. These results indicate that DCA can reverse sustained increases in glucose Ra, recycling and plasma lactate which are consistant with the reported sepsis-induced decrease in PDH activity. (Supported by NIH GM 32654).

182 EFFECTS OF VISCOSITY (η) AND ONCOTIC PRESSURE (π) ON THE FUNCTION OF ISOLATED PERFUSED RAT KIDNEYS (IPRK). B.E. Sumpio, G.R. Upchurch*, D. Kaiser*, J.T. Adkinson*, G.W. Palladino*, G. Johnson* Univ. of North Carolina, Chapel Hill, NC 27514

The influence of perfusate η and π on organ function is not clearly defined. To study this, IPRK were perfused at 37°C at 100 mmHg pressure for 100 min in a Krebs solution containing either 0, 2.5, or 7.5 albumin (A), 0, 10, or 20% Hct blood, substrates and ^{3}H inulin (glomerular marker). Perfusate and timed urine samples were collected and analyzed for radioactivity and [Na^{+}]. Perfusate η (centipoise) was measured on a cone and plate viscometer and π (mmHg) on a vapor pressure osmometer. Tissue ATP (umole/g) was measured enzymatically. The functional parameters: glomerular filtration rate (GFR,ml/min), reabsorption of Na^{+} (FR_{Na},%) and H_2O (FR_{H2O},%), renal perfusate flow (RPF,ml/min), and urine flow (U,ul/min) are given as a means ± SEM for n=27 clearance periods in each group.

Solution	GFR	FR_{Na}	FR_{H2O}	U	RPF	η	π	ATP
0A/0Hct	568 ± 15	41 ± 3	44 ± 3	314 ± 15	34 ± 1	2.9 ± .1	0	.4 ± .1
2.5%A	1054 ± 38	80 ± 1	79 ± 1	215 ± 4	27 ± 1	3.4 ± .2	10.6	.6 ± .2
2.5%A+10% Hct	444 ± 57	70 ± 2	87 ± 2	71 ± 3	5 ± 1	4.1 ± .1	12.6	1.0 ± .3
2.5%A+20% Hct	16 ± 2	21 ± 3	30 ± 2	10 ± 1	1 ± 1	5.6 ± .1	14.2	.4 ± .1
7.5%A	681 ± 65	91 ± 3	87 ± 4	151 ± 13	25 ± 1	3.5 ± .1	43.2	.6 ± .2
7.5%A+10% Hct	406 ± 49	89 ± 9	91 ± 9	34 ± 3	3 ± 1	3.8 ± .1	38.2	.4 ± .1
7.5%A+20% Hct	326 ± 54	75 ± 2	75 ± 2	33 ± 2	2 ± 1	5.7 ± .2	42.4	.5 ± .1

The results show that η significantly affects RPF, U, and GFR while π mainly affects FR_{Na}, FR_{H2O}, and ATP. We conclude that perfusate η and π play independent roles in influencing organ function.

183 INDUCTION OF PDH INACTIVATION FACTOR IN SKELETAL MUSCLE DOWN-REGULATION OF GLUCOSE OXIDATION IN SEPSIS. Thomas C. Vary, John H. Siegel, Ben D. Tall*, J. Glenn Morris*. MIEMSS and Depts. Physiol., Surgery and Geographic Med., Univ. MD, Baltimore, MD 21201

Chronic sepsis lowers the proportion of active pyruvate dehydrogenase complex (PDH) in skeletal muscle. To determine whether sepsis increases PDH kinase activity, rate constants for inactivation of the PDH complex by ATP in skeletal muscle mitochondrial extracts from control, sterile inflammatory and septic abscess rats were determined. Mitochondria were isolated and extracted five days following the intraperitoneal introduction of a fecal-agar pellet with known bacteria which generated an abscess (sterile vs. *B. fragilis* 10^{8}/ml+*E. coli* 10^{4}/ml). The rate constant for inactivation following addition of 0.3mM ATP in control animals was -0.424 min^{-1}(r^2=.993,p<.001) and was not altered in extracts from sterile inflammatory animals (-0.430 min^{-1}; r^2=.999, p<.001). However, the rate constant for ATP inactivation in septic animals was significantly increased over 2-fold to -1.083 min^{-1} (r^2=.987, p<.001) (p<.001 vs control or sterile inflammation). In the presence of PDH kinase inhibitors, either 2.5 mM pyruvate or 1 mM dichloroacetate,

the extent of ATP inactivation was greater in mitochondrial extracts from septic skeletal muscle than either control or sterile inflammation. These data suggests that sepsis, but not sterile inflammation, induces a stable factor in skeletal muscle mitochondria which increases PDH kinase activity and inactivates PDH. This factor appears similar to the kinase activator protein described for starvation and diabetes-induced inactivation of PDH complex. (Supported by NIGMS Grant GM36139)

184 DIFFERENCES OF HEPATIC MITOCHONDRIAL RESPONSE AND ENERGY METABOLISM IN HYPOXIA BETWEEN NORMAL AND CIRRHOTIC RATS. S.Wakashiro*, Y.Shimahara*, I.Ikai*, Y.Tokunaga*, A.Tanaka*, T.Morimoto*, Y.Kamiyama, and K.Ozawa* Second Department of Surgery, Faculty of Medicine, Kyoto University, Kyoto 606, Japan

Influences of hypoxia on hepatic mitochondrial function and energy metabolism were studied in normal and CCl4-induced cirrhotic rats. Rats were placed in a chamber where FIO_2 was adjusted to 10%. After 60 min of the hypoxia hepatic energy charge (EC) of the normal and cirrhotic rats decreased from 0.87 to 0.77, and from 0.79 to 0.75 respectively. The hepatic ketone body ratio (KBR), which reflects mitochondrial redox state, also decreased significantly from 0.65 to 0.37 in normal rats, and from 0.45 to 0.25 in cirrhotic rats. However, oxidative phosphorylation activity (PR:ATP synthesis) of the isolated hepatic mitochondria increased to 123% of the values before hypoxia in the normal rats, while it remained unchanged in the cirrhotic rats. After the 60 min-hypoxia, the FIO_2 of the chamber was normalized to that of room air. The EC of the normal rats was restored to 0.87 already at 5 min after the reverse from hypoxia, concomitant with a significant elevation of the KBR to 1.15. The PR exhibited 153% of the control level after the reverse from hypoxia. On the other hand, the EC of the cirrhotic rats showed 0.81 at 5 min, with the KBR of 0.47. The PR remained unchanged. In conclusions, the energy metabolism of the liver in hypoxia was severely deteriorated both in normal and cirrhotic rats. In normal rats it could be immediately normalized by an enhancement of mitochondrial functions after the reverse of hypoxia. In cirrhotic rats, however, the mitochondrial enhancement was not observed. The absence of the mitochondrial enhancement might be related to a state of lower resistance for hypoxic episode in cirrhotic patients.

185 EVALUATION OF BASAL AND GLUCAGON-STIMULATABLE INSULIN LEVELS IN THE ENDOTOXIC DEVELOPING NEWBORN RAT. W.P. Zeller,* M. Goto, J.P. Filkins, and R.M. Hurley*, Departments of Pediatrics and Physiology, Loyola Univ, Stritch Schl of Med, Maywood, IL 60153.

Glucose dyshomeostasis as manifested by hyper and hypoglycemia occurs in newborn and adult endotoxicosis. While insulin's role in the hypoglycemia of adult endotoxicosis has been well defined, basal insulin changes and their role in the developing newborn are not well established. 10 day old, 4 hour fasted Sprague-Dawley rats were injected with S.enteritidis endotoxin (LPS) 0.1 mg/kg IP ED90 @24 hrs or saline. Glucose mg/dl) and insulin (μU/ml) were analyzed by standard techniques. LPS provoked hyperglycemia as compared to saline controls (n=55) at 2 hrs..112±4 vs 88±2 ($p<.05$) and hypoglycemia at 4 hrs..52±3 vs 73±2 ($p<0.05$). Insulin concentrations in LPS and saline groups were not different(n=11) at 2 hrs, 16±1 vs 17±2 at 4 hrs, 15±2 vs 21±3. Glucagon stimulatable insulin was then measured 2 hrs post the above stated doses of LPS or saline utilizing glucagon(300ug/kg IP)to evaluate the newborn rat pancreatic B-cell maturity. Glucose and insulin (see table) were measured at 15 minute intervals for 2 hours.

	0 (Min.)	15	30	45	60
LPS	17±2 μU/ml	49±11	95±21	78±14	86±18
Saline	16±1	55±13	92±21	78±25	89±34

Basal and stimulatable insulin values were not elevated by LPS. Insulin was equally stimulated by glucagon in newborn rats. Insulin's role in the developing newborn's endotoxicosis and hypoglycemia appears different from adult rats. This difference may be related to newborn rat development. (Support HL-31163)

186 THERMOGENESIS RESPONSE TO COOL FLUID RESUSCITATION: AN EXPLANATION FOR CARDIAC OUTPUT(CO)/OXYGEN CONSUMPTION(VO_2) CONFORMATION DURING FLUID RESUSCITATION. G. Carroll and B. Braverman* Rush Presbyterian St. Luke's Medical Center, Chicago, Il 60612.

Cardiopulmonary function was characterized in 171 patients using standard invasive monitoring techniques. Those with more shock-like illness had more

highly correlated CO and VO_2. Veno arterial admixture (Q_{VA}/QT) was used as an index of shock-like illness. The patients were separated by the median Q_{VA}/Q_T into those with more or less severe illness. Patients with greater than median Q_{VA}/Q_T had CO and VO_2 more highly correlated than those with less than median Q_{VA}/Q_T ($r = .56$ and $.48$, respectively, $p < .01$). Room temperature IV fluid resuscitation was maintained only in the patients in the sicker group during the time when cardiopulmonary measurements were being made. Thus, artifacts in the clinical method may have accounted for part of the association. However, 9 patients had r values greater than .8, of which 5 were above .9. In curarized dogs, we found that CO increases produced by infusion of 20°c crystalloid produced greater increases in VO_2 than did CO increases induced with Diazoxide. We conclude that the occasional patient in shock, who exhibits oxygen conformity during fluid resuscitation, simply may be exhibiting an unusually vigorous thermogenesis response to cool intravenous fluid.

187 GLUCOREGULATORY EFFECTS OF HUMAN NATURAL INTERLEUKIN-1 (IL-1). N. A. Sacco*, M. A. Kordyban*, E. A. McCulla*, M. R. Yelich, J. P. Filkins. Dept. of Physiology, Loyola University Medical Center, Maywood, IL 60153.

It has been hypothesized that monokines, such as Il-1, play a role in mediating carbohydrate dyshomeostasis during septic shock. Thus, the glucoregulatory role of human natural Il-1 (Collaborative Research, MA.) was evaluated in fed(F) and 24h fasted(f) male Holtzman rats (360±14g) with and without glucose(G)-challenge. Rats were anesthetized (sodium pentobarbital) and separated into the following IV treatment protocols: n=4/grp; 1) saline; 2) 25U Il-1; 3) 50U Il-1; 4) 100U Il-1; 5) 400mg G; 6) G + 25U Il-1; 7) G + 50U Il-1; 8) G + 100U Il-1. Sequential plasma G and lactate(L) samples were obtained for 30 min at 5 min intervals. Immunoreactive insulin (IRI) was evaluated at 0 and 30 min. At 30 min, IRI levels were significantly increased ($p<0.05$) in F rats given Il-1 alone (F1: 37 ± 1.6; F2: 66.3 ± 7.8; F3: 67.9 ± 5.7; F4: 100.5 ± 11.6uU/ml). A similar increase was observed in the f4 grp (f1: 21.4 ± 1.0; f4: 53.9 ± 5.5uU/ml). No changes in G or L levels occurred in these grps. F and f G-challenged rats given 50 or 100U Il-1 had significantly decreased G clearance half-times (T1/2) compared to rats given G only (T1/2: F5 = 26 ± 2.5; F7 = 16.5 ± 1.5; F8 = 18 ± 2.0 min; f5 = 18 ± 1.5; f7 = 10 ± 2.8; f8 = 12 ± 1.7 min). T1/2 differences may be associated with increased G induced insulin response in rats given G + Il-1. In conclusion, natural human Il-1 potentiated G-clearance and altered insulin levels even without G-challenge. This study further supports the hypothesis that Il-1 may play a role in mediating G dyshomeostasis during sepsis. (Supported by NIH grant HL31163)

188 TRIMER OF 15-DEHYDRO-PGB_1 IMPROVES RECOVERY OF MITOCHONDRIAL FUNCTION AFTER RENAL ISCHEMIA. Linda L. Widener, Dagmar Bartos and Leena Mela-Riker, Departments of Surgery, Biochemistry and Pediatrics, Oregon Health Sci. Univ., Portland, OR.

Oligomeric mixtures of prostaglandin B_1 are protective against mitochondrial functional failure after tissue ischemia. The active component of the PGB_1 mixture is unknown. We used the trimer of 15-dehydro-PGB_1 to test its protective effect in renal ischemia. Renal ischemia was induced by a unilateral closure of the renal artery in the rat. After a 45 min. ischemic period the arterial clip was opened to recover renal blood flow. At this time the treated animals received a bolus of 2.5 mg/kg 15-dehydro-PGB_1, IP. The untreated animals received an injection of the vehicle. The animals were sacrificed after 24 hours, renal mitochondria were isolated and their function analyzed. The data are shown in the Table.

*p < 0.05	[CYTOCHROME] n moles/mg			STATE 3 RATE moles O_2/mole aa_3/min	
	aa_3	b	c	pyruvate	β-OH butyrate
CONTROL	0.24±.03	0.22±.03	0.63±.1	158±23	146±28
ISCH 45 MIN	0.13±.02*	0.23±.002	0.30±.08*	87±5*	74±19*
24 - PGB_1	0.17±.04*	0.19±.03	0.47±.06*	63±31*	76±41*
HRS + PGB_1	0.19±.01	0.22±.03	0.51±.05	102±28*	115±30

These data indicate that a bolus injection of the trimer of 15-dehydro-PGB_1 given at the time of reflow provides significant improvement of mitochondrial function after 45 min of renal ischemia in the rat. Supported by Office of Naval Research.

189 LEFT VENTRICULAR PERFORMANCE IN CANINE ENDOTOXIN SHOCK. E. J. Papadakis* and E. L. Abel. University of South Carolina Sch. Med., Columbia, SC 29208.

Left ventricular performance was studied in 7 open-chest, heart-paced dogs before and after a single 1 mg/kg BW dose of E. coli endotoxin under pentobarbital anesthesia. + dp/dt max, time to peak ventricular pressure (PVP time), cardiac output, stroke work, tension-time index (TTI), coronary flow and cardiac oxygen consumption were derived from left ventricular pressure, aortic flow, left atrial pressure, coronary sinus flow and A-V oxygen difference which were continuously recorded for up to three hours post-endotoxin. A reservoir with cross-matched blood was attached to the left atrium and the inflow to the atrium was varied periodically, while the afterload was kept constant at two different levels of 60 and 80 mmHg, in order to obtain ventricular function curves for the different variables. Data collected were analyzed statistically with the Randomized Block design method using Tukey's method for multiple pairwise comparisons and unbalanced design. Ventricular contractility assessed by + dp/dt max, PVP time, cardiac output, stroke work and TTI was depressed at the time intervals studied (0-20, 20-60, 60-120 minutes after endotoxin). + dp/dt max was statistically significant at high end-ventricular diastolic pressures during endotoxemia compared to the control period. The findings indicate the presence of early and sustained depression of ventricular performance during endotoxin shock from either a direct or an indirect effect of endotoxin on the myocardium. Supported by grants from South Carolina Heart Association and from Upjohn Company.

190 HEPARIN'S EFFECT ON THE NATURAL HISTORY OF SEPSIS IN THE RAT. William J. Schirmer*, James M. Schirmer*, George B. Naff*, and Donald E. Fry. Departments of Surgery and Medicine, V. A. Medical Center and Case Western Reserve University, Cleveland, OH.

Overactivation of inflammatory and hemostatic systems in sepsis may lead to organ failure and death. This study was undertaken to determine how heparin (HEP) affected the natural history of murine peritonitis. Rats underwent either cecal ligation and puncture (CLP) or sham operation (SHAM). Each group was divided to receive continuous intravenous infusions of either HEP (25 units/kg/hr) or saline (SAL)(0.01 ml/hr) via subcutaneous osmotic minipumps. Thermodilution cardiac output (CO), hematocrit (HCT), effective hepatic blood flow (EHBF) by galactose clearance, and effective renal blood flow (ERBF) by PAH clearance were measured at 18 hrs. Survival curves were generated from n=12 rats in both SAL and HEP treated CLP groups. Data as mean(±SEM):

		FLOW DATA (ml/min/100gm body wt)			SURVIVAL (#alive/n)	
GROUP-INFUSION(n)	HCT(%)	CO	EHBF	ERBF	60 hrs	120 hrs
SHAM-SAL (n=16)	44.4±0.8	35.6±1.5	4.32±0.18	4.77±0.24	--	--
SHAM-HEP (n=8)	42.8±1.2	38.8±2.0	4.99±0.30	5.49±0.59	--	--
CLP-SAL (n=15)	44.7±1.0	32.9±1.4	3.33±0.18*°	3.43±0.18*	9/12	2/12
CLP-HEP (n=8)	41.1±1.8	32.9±1.5	4.19±0.40	3.56±0.18*	11/12	8/12"

*p<.05 vs SHAM-SAL & °p<.05 vs CLP-HEP by ANOVA. "p<.05 vs CLP-SAL by Mantel-Cox.

Critical reductions (p<.05) were also noted in the amount of fibrin degradation and degree of complement activation in the CLP-HEP group relative to CLP-SAL. The animals may have derived survival benefits from heparin due to its ability to preserve visceral flow in sepsis thereby averting organ failure.

191 ROLE OF CALCIUM IN IMPAIRMENT OF INSULIN-MEDIATED SKELETAL MUSCLE SUGAR TRANSPORT DURING BACTEREMIA. M.Westfall*,M.Sayeed. Dept.Physiol.,Loyola Univ.,Maywood,IL60153.

Sepsis impairs insulin-mediated glucose utilization in skeletal muscle which might result from altered membrane sugar transport. In this study, we characterized the insulin dose-dependency of sugar transport during bacteremia and evaluated if cellular Ca^{2+} overload was responsible for the altered insulin response. Sugar transport was measured in soleus muscles using 3-O-methylglucose (3MG) efflux from fasted rats(90g) injected with saline (C) or E. coli ($4x10^{10}$ CFU/kg,B) 12 hrs prior to removing muscles. Muscles were loaded with ^{14}C-3MG in KRB and then sequentially washed in radioisotope-free media with insulin (0.1-10mU/ml). Media and muscle radioactivity were used to calculate effluxes (λ, min^{-1}). Increased basal efflux occurred in bacteremic muscles ($C\lambda$=0.019±0.001,n=54;$B\lambda$=0.022±0.001,n=48) and could have contributed to the elevated transport observed in these muscles with 0.1mU/ml insulin (C=0.032±0.003,B=0.046±0.003,n=8). However, 3MG transport was attenuated in bacteremic rat muscles incubated with 1.0^a or 10^bmU/ml insulin compared to controls (B^a=0.042±0.004,B^b=0.050±0.003;Ca=

0.058±0.004,C[b]=0.060±0.003,n=8). Ionophore A23187 (INO,1μM) was added to mimic Ca^{2+} overload in controls and to potentially enhance any overload in bacteremic muscles.

	C,-INO (λ)	C,+INO (λ)	B,-INO (λ)	B,+INO (λ)
Basal	0.019±0.001(8)	0.020±0.001(8)	0.023±0.001(9)	0.022±0.001(8)
Insulin10mU/ml	0.046±0.002(8)	0.039±0.002[a](8)	0.039±0.001[b](9)	0.035±0.003(8)

()=# of expts.;λ=min^{-1}; [a]p 0.05 compared to no INO; [b]p 0.05 compared to control

INO attenuated insulin-mediated 3MG transport in control muscles but had no further effect on bacteremic muscles. The data support the idea that Ca^{2+} overload decreases insulin-stimulated sugar transport during sepsis. Support:NIH Grant GM32288 &HL31163.

192 THE ROLE OF MULTIPLE FACTORS IN THE PATHOGENESIS OF SEPTIC AND ENDOTOXIC SHOCK

Hua-cui CHEN, Heng-yi GUO, Dian-mo XIAO, Shu-huai XU and Zhen-yan LIU

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Serum complement C_3, fibrin degradation product and plasma PGE, $PGF_{2\alpha}$, cAMP, cGMP, urinary catecholamines, histamine, serotonin were studied in a series of cases of septic shock due to fulminant meningococcal meningitis with more prominant changes in septic shock form than in ordinary form of the disease. To further explore such findings, plasma catecholamines(noradrenaline, adrenaline, dopamine), angiotensin II, prostaglandins(PGE, $PGF_{2\alpha}$, TXA_2), serotonin and red blood cell acetylcholinesterase were studied in canine endotoxic shock. Other small animal models served as supplemental studies in noradrenaline histofluorescence intensity and tissue acetylcholine concentration. The results indicated that the activation of the sympathetic nervous system in this model might not be the causal factor but instead secondary or reflexive in nature. There are multiple humoral factors which involved in the pathogenesis of shock, their 'net effect' may be important in shaping the underlying hemodynamic features.

193 THE MECHANISM OF INHIBITION OF ANISODAMINE ON PLATELET AGGREGATION INDUCED BY E. COLI ENDOTOXIN. Shu-Huai Xu, Guang-Jin Zhu, Qi-Xia Wu and Hua-Cui Chen (Spon: Maw-Shung Liu). Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences, Beijing, China.

The platelet aggregation induced by E. Coli endotoxin both in vivo and in vitro studies in rabbit were observed by modified Wu and Hoak's method,SEM and turbidimetry In vivo studies, the PACR was 0.84±0.06 before ET injection and 0.52±0.07 after injection ($p<0.01$). After 5-20' anisodamine (654) intervention, PACR was increased to 0.83±0.08, the aggregated platelets became partially dispersed and the pseudopods shortened and thickened. In vitro studies, in the presence of ET, it made the platelet aggregation and the level of cAMP decreased (3.48±0.19 pmol/10^9) in comparison with control (5.45±0.19, $p<0.001$). The induced platelet aggregation was inhibited together with increased cellular cAMP by intervention of anisodamine from 3.48±0.19 to 4.87±0.52 pmol/10^9. Whereas in the case of anisodamine alone the cellular cAMP obviously increased from 5.45±0.19 pmol/10^9 to 7.61±0.34 pmol/10^9, $p<0.001$.

194 EFFECT OF ANISODAMINE ON ARACHIDONIC ACID METABOLISM IN SEPTIC RATS. Yung-ping Tao, Dian-mo Xiao and Hua-cui Chen. Department of Pathophysiology, Peking Union Medical College, Beijing, CHINA

Anisodamine, an alkaloid which is mainly a cholinergic M-receptor antagonist, has widely been used as an antishock drug in China for two decades. This study attempted to determine if anisodamine affects arachidonic acid metabolism in rat septic shock induced by cecal ligation with punctures. Anisodamine was injected i.v. at a dose of 10 mg/Kg/hr for 5 hrs, starting at 4 hrs after the operation. The survival time in rats treated with anisodamine was prolonged(24.3±2.2 hrs,

P<0.05 vs control, 19.8±0.6 hrs) and the changes of mean arterial blood pressure (MABP), plasma levels of thromboxane B_2(TXB_2) and 6-keto-prostaglandin $F_{1\alpha}$(6-K-$PGF_{1\alpha}$) were following:

		Hours post-operation			
		0	6	12	16
Control(20)	MABP(mmHg)	112±2	95±3*	71±2*	46±4*
	TXB_2(pg/ml)	321±16	707±68*	453±54	282±16
	6-K-$PGF_{1\alpha}$(pg/ml)	174±12	224±26*	431±37*	1158±130*
Anisodamine(10)	MABP(mmHg)	112±2	107±6 △	89±8 △	66±4 △
	TXB_2(pg/ml)	321±16	373±64 △	401±78	446±84 △
	6-K-$PGF_{1\alpha}$(pg/ml)	174±12	371±69	420±51	832±127

* P<0.05 vs time=0; △P<0.05 vs Control.

These data suggested that the beneficial effects of anisodamine on septic rats may partly resulted from inhibition of TXA_2 synthesis.

195 VERAPAMIL INDUCED HYPERCOAGULABILITY IN VITRO. C. Spillert, A. Razac*, W. Suval*, and E. Lazaro*. UMD-New Jersey Medical School, Newark, NJ, 07103-2757.

Verapamil, a calcium entry blocker, has been reported to be efficacious in canine endotoxic shock. This beneficial effect has been attributed, in part at least, to antiplatelet cardioprotective mechanisms. However, the role of verapamil in the clotting process has not been documented. Whether verapamil can prolong recalcification times (RT) of human plasma in vitro (anticoagulant effects) in the presence of procoagulant tissue factor (TF) which is generated early in shock, was the purpose of this study. A 1cc aliquot of human citrated plasma (n=8) was incubated with verapamil at final concentrations of 0, 125, 400 and 4000 ng/cc for 10 min. Then either saline (control) or tissue factor was added and the RT determined. The mean RT (mins) ± SD for the two agents (saline and TF) in varying concentrations of verapamil are tabulated below:

Agents	Mean RT±SD Verapamil Concentrations (ng/cc) 0	10	40	4000
Saline (10µl)	(A) 11.9±3.2	(B) 11.7±1.7	(C) 11.0±1.9	(D) 11.7±2.7
TF (2.5 µg/cc)	(E) 6.6±1.5	(F) 5.4±1.2*	(G) 5.9±0.9*	(H) 6.3±1.1

*p<.05 F and G vs E

Conclusions: (1) Verapamil has no effect on RT in the absence of TF. (2) Verapamil potentiates the hypercoagulable state induced by TF (reduces RT).

196 **GRAM NEGATIVE PNEUMONIA PRODUCES A HYPERDYNAMIC SEPTIC SHOCK SYNDROME.** **R.KEENAN*, T.TODD & M. GIROTTI. SURGICAL INTENSIVE CARE UNIT, TORONTO GENERAL HOSPITAL. TORONTO, ONT. M5G 1L7.**

General anaesthesia (GA) and extensive surgery used to reproduce a hyperdynamic shock syndrome (HSSS) may confound the observed effects of pure HSSS. A large animal model of HSSS without GA or extensive surgery in 10 adult hemodynamically instrumented sheep (wt. 25-30kgs.) was created by direct bronchoscopic instillation of 10(8)-10(10) Pseudomonas aeroginosa organisms into the left lower lobe. These procedures were carried out with light ketamine/lidocaine anaesthesia. Cardiopulmonary measurements were done prior to induction of pneumonia (B), and 24 hours after pneumonia (HSSS) with animals awake and spontaneously breathing. Standard hematology and blood cultures were drawn. Table I summarizes results. During HSSS all animals were pyrexic, developed a significant leukocytosis and had positive pseudomonas blood cultures.

TABLE I

	B	HSS		B	HSS	
C.O.(L/min)	**5.0±0.9**	**6.3±1.1***	**PAP**	**16±3**	**20±4***	
SVR	**142±205**	**1000±245***	**Ca-vO2**	**2.9±0.7**	**2.04±.4***	***p<0.05**
PVR	**128±43**	**157±50***	**VO2**	**142±34**	**127±38**	**paired**
MEAN BP	**93±10**	**82±10***	**O2 Del.**	**675±102**	**779±143**	**T-test**

We conclude that Psuedomonas pneumonia in awake sheep produces a non lethal, HSSS similar to that observed in man.

197 MYOCARDIAL DYSFUNCTION IN EARLY GUINEA PIG ENDOTOXICOSIS: LACK OF PROTECTION BY NALOXONE. R.S. Keller*, L.L. Behm,* H.R. Adams, and J.L. Parker. Dalton Research Center and Dept. Veterinary Biomedical Sci., Univ. of Missouri, Columbia, MO 65211.

Isolated heart preparations were used to evaluate potential beneficial myocardial actions of naloxone in early non-hypotensive endotoxicosis in guinea pigs. Experiments were conducted 2-3 days following chronic instrumentation of animals for measurement of *in vivo* hemodynamic parameters. Animals received 1 mg/kg IP purified *E. coli* endotoxin (ET), and immediately treated with either naloxone (NAL) (4 mg/kg IV bolus plus 4 mg/kg/hr infusion; n=8) or saline (SAL) (n=7). Control animals were also treated with either NAL (n=4) or SAL (n=7). Hearts were isolated 4 hrs post-ET and coronary-perfused for *in vitro* analysis of myocardial function. Hemodynamic parameters in all groups remained normal during the 4 hr observation period. However, ET produced hypothermia, increased arterial PO_2 and pH, and decreased PCO_2, which were unaltered by NAL. Importantly, ET administration produced significant myocardial dysfunction and reduced left ventricular (LV) function curves of isolated hearts, which was not prevented or reduced by NAL. For instance, developed LV pressure (LV end-diastolic pressure=14 mmHg) averaged 71±2 and 74±6 mmHg, respectively, in hearts from SAL and NAL treated control animals, and 33±1 and 36±1 mmHg in hearts from SAL and NAL treated ET animals. Reduced inotropic responses to increasing perfusate Ca^{++} concentrations (1-8 mM) observed in ET hearts was not reversed in ET hearts treated with NAL. We conclude that intrinsic, myocardial dysfunction in early, non-hypotensive endotoxicosis is not improved by opioid receptor blockade with NAL. (Supported by NIH RCDA HL-01669 and American Heart Assoc.)

198 REDUCED LABELING OF HEPATOCYTE PHOSPHOLIPIDS BY ^{14}C-ARACHIDONIC ACID (20:4) AND LOW ACCUMULATION OF ^{14}C 20:4-DIACYLGLYCEROL UPON VASOPRESSIN (VP) STIMULATION IN CHRONIC NON-LETHAL ENDOTOXEMIA. E. Rodriguez de Turco and J.A. Spitzer, Dept. of Physiol., Louisiana State University Medical Center, New Orleans, LA 70112.

We studied arachidonic acid (AA) metabolism in hepatocytes from rats continuously infused iv with saline (SAL) or E *coli* endotoxin (ET) for 30 h (Fish and Spitzer, Circ. Shock 12:135-149, 1984). After 30 min of incubation of SAL-cells with ^{14}C-AA, 5% remains in the free fatty acid (FFA) pool, 28% of the added precursor is esterified in triacylglycerol (TG) and 30% in phospholipids (PLs). In ET cells the removal of ^{14}C-AA from the FFA pool is very slow. After 30 min, 21% is recovered in the FFA pool, while 50% can be accounted for by esterification in TG (29%) and PLs (21%). A significant proportion of the added precursor (39 and 29% for Sal and ET cells, respectively) was not recovered in the lipid pools analysed and could reflect the oxidative capacity of the cells when AA is the substrate. Hence, a low activity of acyl-CoA ligase and/or acyltransferase during endotoxicosis a) could affect active turnover of membrane AA-PLs, b) could increase the availability of AA for eicosanoid synthesis. The metabolism of ^{14}C-AA-containing PLs was analysed in cells that had been prelabeled with ^{14}C-AA for 30 min. Upon continuous VP stimulation of ET cells for 5-10 min, ^{14}C-AA-diacylglycerol accumulation was 65% lower than in SAL cells. The pattern of lipid changes was similar to that observed when the content of DG and AA were quantitated by GLC. These alterations in the uptake of AA and in the metabolism of AA containing lipids could contribute to cellular metabolic perturbations in endotoxicosis. Supported by NIH grants GM32654 & GM30312.

199 HEMODYNAMIC MEDIATORS IN HYPERDYNAMIC ENDOTOXICOSIS: LIMITED ROLE OF PROSTAGLANDINS (PG) AND THROMBOXANE (Tx). M. Fink, K. Stein*, P. Morrissey*, R. Clement*, V. Fiallo*, W. Gardiner*, Univ. Massachusetts, Worcester, MA 01605.

Rabbits were injected iv with saline (NS) or endotoxin (LPS; 1-3 ug/kg) and studied 4-6 h later. Cardiac index (CI; ml/min/kg) and regional blood flow (ml/min/100 g) were determined using thermodilution and radioactive microspheres, respectively. After obtaining baseline hemodynamics, rabbits received indomethacin (IN; 5 mg/kg), UK38485 (Tx synthetase inhibitor; 10 mg/kg), or NS. Data were acquired again 40 min later. Drug effects were assessed by repeated measures ANOVA. Shown are p values for "D" (effect of drug, independent of group) and "GxD" (interaction

of drug effect with pretreatment group). Results below are means±SE. * indicates $p<.05$ vs NS group. Systemic vascular resistance index (SVRI) expressed as torr·min·kg/l. UK38485 and NS had minimal effects regardless of group.

		all NS (n=18)	all LPS (n=24)	IN→NS (n=8)	IN→LPS (n=12)	"D"	"GxD"
CI	Pre-IN	237± 7	284± 5*	236± 8	281± 8	.009	.057
	Post-IN			230± 9	250±14		
SVRI	Pre-IN	418±16	302± 5*	414±14	300± 8	.003	.160
	Post-IN			453±21	395±27		
GUT FLOW	Pre-IN	91±10	131±12*	78±11	100±13	.004	.498
	Post-IN			61±12	74± 6		

Although IN decreased CI and increased vascular resistance in hyperdynamic endotoxic animals, this drug caused similar (albeit smaller) changes in controls. Thus, non-PG mediators are probably important causes of decreased vasomotor tone in sepsis.

200 OXYRADICAL FORMATION IN ENDOTOXIN SHOCK. C.M. Jabs, P. Neglen and B. Eklof. Faculty of Medicine, Kuwait University, Kuwait.

Enthusiasm exists today on the mechanism of oxygen derived free radical tissue damage in shock. One source of radicals is adenine nucleotide breakdown. Non-polar intermediates such as adenosine, inosine, and hypoxanthine (Hyp) may accumulate during shock and become available to tissue and extracellular fluid inflicting cellular injury. We determined whether plasma rises of these dangerous oxygen forming intermediates in shock reflect the severity of endothelial injury and leakage. We evaluated plasma high-energy phosphagens and breakdown products during E. coli endotoxin shock (4mg/Kg) in rabbits until death 14 ± 3 hours later. In late shock the plasma adenosine 5' triphosphate (ATP) level dropped as expected to 8% normal indicating a low cellular content. Concentrations of all other measured metabolites showed significant rises: Adenosine 5' diphosphate (ADP)(191%), creatine phosphate (CrP)(689%), creatine (Cr)(1128%), creatinine (146%), inosine (1532%), Hyp (1630%) and lactate (935%), respectively. The only metabolite showing an early significant increase was Hyp (314%) at 5 minutes after the injection of endotoxin, during the initial platelet aggregation phase. This early leakage may permit the entry of endotoxin into the intracellular compartment. As platelets deaggregate and approached 50% of normal, Hyp concentration decreased, but remained doubled for 7 hours. Cr, CrP, inosine, and lactate showed a continuous steady increase the first 7 hours until leakage became major. This occurred after lactate levels surpassed 7 mmol/l, indicating a crucial aerobic metabolic deficiency. This tissue inhibition appears to make adenine breakdown intermediates available to plasma. The early plasma rise of Hyp indicated early endothelial injury and its constant elevation may be involved in causing progressive damage by producing oxygen radicals in its breakdown. The early and gradual rise of other metabolites not normally present in plasma suggest progressive membrane injury. Our present evidence suggest that ATP catabolism may be involved in oxyradical formation.

201 THE USE OF FREE RADICAL SCAVENGERS IN RAT PERITONITIS. W. Limm* and J. J. McNamara, University of Hawaii School of Medicine, Honolulu, Hawaii 96813

In the early 1960's Davis and Yull noted a synergistic effect on mortality with injection of E. Coli. and red blood cells into rat peritonium. Since then their model has proven to be remarkably consistent. However, except for the implication of iron as the critical agent, minimal progress has been made in explaining the lethality of this combination. Furthermore, no treatment has been found that affects the outcome. The hypothesis that the adjuvant effect of Hemoglobin (Hgb) may be mediated by oxygen free radicals was tested by treating infected rats with free radical scavengers. Hgb is a known catalyst of the Fenton reaction. The product of this reaction is the toxic hydroxyl radical. Sprague Dawley rats weighing 180-250 gm were injected with broth containing E. Coli. and Hgb in concentrations identical to that of Davis and Yull. Each animal received a total volume of 5 cc/kg. The treated animals received superoxide dismutase (SOD: 2,600 units/kg) and catalase (11,000 units/kg) or mannitol (.7 g/kg) in the broth mixture. The mortality rate for the E. Coli/Hgb mixture was 80% (n=10). E. Coli. alone had a mortality rate of 17% (n=6). The mortality rate was significantly reduced by mannitol 5/12 (42%, $p<.05$) and SOD/catalase 3/10 (30%, $p<.025$). Bacterial counts after 24 hr incubation at 37°C were not altered by the addition of SOD/catalase or mannitol. SOD/catalase and mannitol may be able to significantly modify the lethal combination of E. Coli. and Hgb in rat peritonitis. This beneficial effect may be secondary to their ability to scavenge free radicals.

202 A NEW METHOD:M.S.S.(Milan Sepsis Score) TO EVALUATE THE SEVERITY OF SEPSIS. A. Nespoli*, P. Padalino*, O. Chiara*, M. Gardinali*, M. Prandinelli* and G. Bevilacqua*. (Spon L.B. Hinshaw). Institute of Emergency Surgery, Franceso Sforza 33, University of Milan, Milan, Italy.

A prospective study was carried out in 8 severely septic patients (mean age: 40, range 26-69) in order to evaluate the seriousness of sepsis. All patients had positive blood cultures and 4 died because of multiple system organ failure. Our method, based on 15 parameters, was planned to identify respiratory, cardio-circulatory and metabolic dysfunction. A value of 0 to 4 was assigned to each variable according to its degree of abnormality and MSS is the sum of assigned weights for all measurements recorded. Four classes were found: Class I:MSS <8, Class II:9-13, Class III:14-18 and Class IV: >19. Complement activation was also investigated by measuring C_{3a} to identify inflammatory response amplitude. 176 determinations of MSS were evaluated and C_{3a} determination was performed only when patients' MSS-Class changed. The mean evaluated time was 6 days for each patient. Patients who survived entered in Class IV but returned to lower classes during recovery, while all patients who died belonged to Class IV in the last monitorings. Markedly abnormal values of C_{3a} were measured in all patients but complement levels returned to normal (300 ng/ml) in patients who survived; on the contrary C_{3a} concentrations remained elevated in patients who died until death (2225± 850 ng/ml). A positive relation between plasma C_{3a} and MSS (R^2:.41, $p < .001$) was found; moreover a good correlation between C_{3a} and classes of MSS was identified (Class I 748 ±205 ng/ml; Class II; 1123 ± 141 ng/ml; Class III: 1721 ± 155 ng/ml; Class IV: 2459 ± 244 ng/ml). All differences are statistically significant ($p < .05$), Class I vs Class II excluded. It is possible to conclude that MSS classification is a valid method to evaluate the severity of sepsis.

203 HEMATOLOGICAL CHANGES INDUCED BY ENDOTOXIN AND PAF IN THE RAT : INHIBITION BY BN 52021. P. Braquet, C. Guilmard, F.Hecquet, C. Soulard and A. Etienne.
I.H.B. Research Labs, 17 avenue Descartes, F-92350 Le Plessis-Robinson (France)

The neutrophil has been strongly implicated in lung and vascular injury occuring after endotoxemia or anaphylactic shock. As PAF was demonstrated to be a key mediator involved in these pathologies and was proved to be a potent stimulant for neutrophils, we studied the hematological changes induced by a systemic injection of PAF or endotoxin in the rat. PAF (1 µg/kg) induced a rapid hemoconcentration (hematocrit + 25 %, red cells count + 24,5 %, platelets + 24 % at time 15 mn) with a further increase in total leucocytes count (+ 64 %) still observable at time 4 hrs (+ 34 %) whereas the other parameters returned to normal values. Differential white cells count showed that the early phase leukocytosis is due to lymphocytes count increase (+ 21 %) with a concomitant decrease in neutrophils count (- 52 %) when reverse variations were observed during the late phase : lymphocytes - 67 %, neutrophils + 215 %. Eosinophils were decreased in the two phases. The hemoconcentration observed after endotoxin injection (S. enteritidis, 12 mg/kg) was lower than that obtained after PAF but differential white cells count varied in the same way after the two agonists. Endotoxin in addition decreased platelets count probably due to disseminated intravascular coagulation. Oral administration of the PAF-antagonist BN 52021 (5-20 mg/kg) partially prevented these hematological changes confirming PAF involment in endotoxin-induced leukocytes mobilization.

204 SELECTIVEE REMOVAL OF ENDOTOXIN FROM THE BLOOD BY EXTRACORPOREAL HEMOPERFUSION WITH POLYMYXIN B IMMOBILIZED FIBER.
T. Tani*, K. Hanasawa*, T. Oka*, T. Yoshioka*, H. Aoki*, Y. Endo* and M. Kodama* (Spon: H. Hirasawa).
First Department of Surgery, Shiga University of Medical Science, Seta Otsu, Shiga, Japan

Endotoxin shock therapy has not been successfully dealt with despite using massive antibiotics or anti-shock drugs. Circulating endotoxin in the blood is an important factor in the pathogenesis and clinical symptoms of endotoxin shock. We have recently developed the Polymyxin B Immobilized Fiber (PMX-F) as a biomaterial for selectively detoxifing endotoxin. In ex vivo experiments, direct hemoperfusion (DHP) by PMX-F was performed for purified endotoxin injected canine. Only 12.5 % (1 of 8) survived in the control group, but 83 % (10 of 12) survived in the group receiving DHP with PMX-F. Mortality in the treated group decreased remarkably. The results thus indicate the efficacy of PMX-F in neutralizing endotoxin. By the same method as

above. DHP with PMX-F was carried out on live Escherichia coli induced septic dogs. All of them died within 18 hours after bacteria infusion in the control group. But all in the treated group survived more than 3 days. Two of the five dogs survived permanently. One of the remaining two survived 7 days and the other 14. We found that PMX-F treatment prolonged or increased survival rate in septic dogs. Deceasing endotoxemia, as a part of the complex therapy, may play a decisive role in saving the patients suffering from serious endotoxin shock and endotoxemia.

205 ALPHA ADRENERGIC BLOCKADE(AAB) ALTERS REGIONAL PERFUSION(RP) DURING LIVE E. COLI BACTEREMIA G. A. Fantini*, S. Shiono*, B. Bal*, J. P. Minei*, G. T. Shires III and G. T. Shires* The New York Hospital-Cornell Medical Center, New York, NY 10021

Pretreatment with alpha adrenergic blocking agents has been purported to improve survival following endotoxin shock, though the underlying mechanisms have remained unclear. The purpose of this experiment was to define the effect of AAB on RP during live E. Coli bacteremia. Sprague-Dawley rats(280-380g) were anesthetized, and tracheostomy with catheterization of jugular vein, femoral artery(FA) and left ventricle performed. Following a one hour equilibration period, 5.3×10^8 live E. Coli organisms/hr were infused into the FA in 0.5ml saline/hr(SEPSIS), while CONTROL rats received saline only at 0.5ml/hr. One hour prior to their respective infusions, AAB was produced in the AAB-CONTROL and AAB-SEPSIS rats with 0.5mg/kg phenoxybenzamine IV, as evidenced by epinephrine reversal. Following 3 hrs, RP(ml/min/g tissue) was determined using ^{51}Cr labelled microspheres(15 micron).

		Stomach	Cecum	Pancreas	Spleen	Portal Vein
CONTROL	(n=7)	0.95±0.14	2.54±0.34	0.82±0.10	3.47±0.37	1.83±0.16
SEPSIS	(n=6)	0.52±0.11*	1.31±0.15*	0.35±0.06*	1.12±0.24*	1.34±0.11*
AAB-CONTROL	(n=5)	0.74±0.15	2.39±0.22	1.17±0.21	3.33±0.29	1.41±0.08
AAB-SEPSIS	(n=5)	0.64±0.07	2.49±0.18	0.48±0.04*	1.88±0.27*	1.62±0.12

*$p < 0.05$ vs. respective control by unpaired t-test; X = mean ± SE.

These data indicate that preexisting AAB alters the vasomotor response to live E. Coli infusion such that stomach, cecal and portal venous (total splanchnic) blood flows are preserved.

206 EFFECT OF R58 735 (A CALCIUM ANTAGONIST) ON THE RESPONSE TO BILATERAL HIND LIMB ISCHAEMIA IN THE RAT. E. ARMSTRONG*, D.W. YATES (Spon: R.A. Little) MRC TRAUMA UNIT, UNIVERSITY OF MANCHESTER, MANCHESTER, U.K.

A change in calcium homeostasis may have a major role in the pathogenesis of the response to injury (Chernow & Roth, Circ Shock 18: 141-155; 1986). For example, flunarizine and R58 735 (Janssen Pharmaceutical Ltd) protect against tissue hypoxia. In the present study the effect of R58 735 (10 mg/kg i.p. given 1 h before tourniquet removal) was studied on the pattern of response to a 4 h period of bilateral hind limb ischaemia in the rat at an ambient temperature of 18-22°C. The drug significantly improved survival at 48 h after injury (drug - 11 survivors from a group of 23: vehicle - 4 survivors from a group of 24; $P<0.05$). The fall in deep body temperature, characteristic of this model of injury, was similar in both groups for the first 2 h after tourniquet removal, but thereafter it was better maintained in the drug treated animals. Preliminary results suggest that the reduction in regional cerebral blood flow, measured by the hydrogen washout technique, are ameliorated by treatment with R58 735.

207 MECHANISMS FOR THE DEVELOPMENT OF FEVER IN YOUNG CHILDREN AFTER BURN INJURY C.CHILDS* (Spon. R.A.Little) BOOTH HALL CHILDRENS HOSPITAL. MANCHESTER.UK

Moderate to severe burns have a profound effect upon body temperature of young children. During the first 12 hours rectal temperature (T_r) rises and fever continues until healing is achieved. Although Paracetamol is reported to be ineffective in lowering T_r in adult burn patients . in children the results are quite different. Paracetamol was administered orally to 29 children (< 3years) with burns covering 10-44% of the body surface when T_r was > 38.5°C. In each case the temperature gradient between core (T_c) and

peripheral skin (T_{toe}) was measured, on administration of the drug and after 6 hours. A large temperature gradient (> 4°C) between T_C and T_{toe} initially was followed by an increase in T_{toe}, a fall in T_r and a reduction in the temperature gradient. However there was no change in the temperature gradient between between T_C and T_{toe} if the initial gradient was small (< 4°C). T_C and T_{toe} fell in parallel. In both groups there was an equal fall in T_C. These results suggest 2 factors in the pathogenesis of the rise in Tc during the early hours of burn injury in these children:a centrally mediated vasoconstriction and in some cases an increase in heat production.

208 ELEVATED PLASMA BETA-ENDORPHINS AND DECREASED MYOCARDIAL PERFORMANCE IN ENDOTOXIC (LPS) SHOCK. S. Doty*, H. Lubbesmeyer*, D. Herndon, D. Traber. U TX Med Br and Shriners Brns Inst, Galveston, TX, 77550.

Myocardial depression is a common finding in sepsis. The purpose of this investigation is to evaluate the relationship between beta-endorphin (pB-E) and myocardial function using an ovine model of sepsis. METHODS: Sheep (N=20) were prepared with Swan-Ganz, left atrial catheters. At one week baseline data were collected, LPS (1.5 ug/Kg x 30 min) given, and the animals studied for 24 hrs. Hemodynamics and pB-E levels were compared between survivors (SS) and non-survivors (NS). RESULTS: Both groups had early decreased stroke work (SWI) and CI. In group SS these returned toward baseline while in group NS they remained decreased. Increased pB-E were likewise noted and they were sustained until death in group NS. LAP did not differ between groups. DISCUSSION: With LPS, SWI and CI depression are temporally related to elevated pB-E and mortality and, given equivalent LAP, seem related to myocardial depression. (Supported by NIH Grant #HL34752)

	CI (liter/min/m2)			SWI (units ml/mmHg)from baseline	
Time(hrs):	0	5	12 or demise	5	12 or demise
SS(N=9)	5.47±0.4	5.00±0.4	6.79±0.3*	-1535±401*	-1372±424*
NS(N=11)	5.67±0.3	3.22±0.4*+	2.84±0.4*+	-2559±440*+	-3162±411*+

pB-E(pcmole/l)Time:	0	2	8	12 + demise
SS(N=6)	6.85±2.1	27.40±7.0*	8.40±2.0	5.35±1.4
NS(N=6)	6.80±1.6	36.69±7.6*	30.85±4.1*+	39.68±4.0*+

DATA (Mean±SEM) *=p<0.05 within groups +=p≤0.05 between groups

209 THE ROLE OF PLATELET-ACTIVATING FACTOR IN GASTROINTESTINAL DAMAGE : A STUDY USING VARIOUS MODELS IN THE RAT. A. Etienne, C. Guilmard, C. Soulard, F. Clostre and P. Braquet.
I.H.B. Research Labs, 17 avenue Descartes, F-92350 Le Plessis-Robinson (France)

Platelet-activating factor (PAF) was recently shown to be a potent ulcerogenic agent in the stomach. As gastrointestinal ulceration is often associated with septic shock, a pathology in which PAF was proved to be involved, we compared the gastrointestinal damage induced by i.v. injection of PAF or endotoxin in the rat. Both agents caused dose-dependent lesions such as hemorrhage associated with vascular congestion of the mucosa of stomach and small intestine, and mucus hypersecretion. Oral pretreatment with BN 52021 (20 and 40 mg/kg), a specific PAF antagonist, markedly decreased alterations induced by PAF (2 µg/kg) and endotoxin (salmonella enteriditis 12 mg/kg), particularly at the intestinal level. BN 52021 was also effective against restraint stress-induced gastric damage whereas it did not affect hypersecretion and ulcerations in pylorus-ligated rats or aspirin-induced ulcerations. The present results indicate a potential therapeutic use of PAF-antagonists in certain types of gastrointestinal lesions.

210 RESPIRATORY QUOTIENT (RQ) OF DIFFERENT ORGANS FROM BLOOD GAS DATA IN SHOCK. I. Giovannini, C. Chiarla, G. Boldrini, M. Castagneto. Centro Studio Fisiopatologia Shock CNR, Catholic University, I-00168 Rome, Italy.

An extensive work was performed in order to develop a method for determining RQ values from O_2 and CO_2 tensions, pH and hematocrit of arterial (a) and venous (v) blood flowing from different body districts. RQ is the ratio of v-a CO_2 (DCO_2) to a-v O_2 concentration gradients, and inaccurate estimation of DCO_2 in conditions of altered physiology has prevented reliable RQ studies in the past. An original model for DCO_2 calculation has been developed on the basis of regression analysis from reference data, iterative and other mathematical procedures. It is used for quantifying different components of CO_2 exchange (Haldane effect, etc.) and has reproduced data from independently obtained actual measurements with a 94-99% control of variability (r^2=0.94-0.99, $p<<0.001$). Extensive preliminary application has allowed easy determinations of muscular, splanchnic and total body RQ (from a, femoral v, portal v and central v blood) in human and experimental sepsis and shock. The model, suitable for use in small desk calculators, is a precious tool for studying substrate utilization and selectively altered metabolic patterns in different organs or districts in shock.

211 EFFECT OF ALTERATIONS IN THE FATTY ACYL COMPOSITION OF INTESTINAL PHOSPHOLIPIDS ON CIRCULATORY SHOCK C.E. Hock, L.D. Beck*, M.A. Holahan* and D.K. Reibel*. University of Medicine and Dentistry of New Jersey - SOM, Camden, NJ 08103 and Thomas Jefferson University, Phila., PA 19107.

Membrane phospholipids (PL) may play an important role in the response of an organ to ischemia. We have evaluated the effect of altering the fatty acyl composition of intestinal PL on the development of circulatory shock induced by superior mesenteric artery occlusion (SMAO) followed by reperfusion (R). Rats were maintained on diets of varying degrees of unsaturation: 1) standard Purina chow (PC), 2) a purified diet containing 7% corn oil (CO) or 3) a purified diet containing 5% menhaden oil (MO) + 2% CO. Anesthetized rats were subjected to two hours of SMAO followed by R. PC fed rats subjected to SMAO exhibited a shock state characterized by a significant reduction in mean arterial blood pressure (MABP) ($p<0.001$), a twelve-fold elevation in plasma cathepsin D activity and a survival time of 1.1 ± 0.3 h. Rats fed the more highly unsaturated diets (i.e., CO or MO + CO) had lower plasma cathepsin D activities ($p<0.001$) and significantly prolonged survival times ($p<0.01$) when compared to PC fed rats. Sixty-two per cent survived at least 4 hours with a MABP of 97 ± 7 mmHg. Rats fed MO + CO but not CO alone exhibited profound changes in the composition of intestinal PL when compared to rats fed PC. Therefore, the anti-shock action does not appear to be correlated with dietary changes in intestinal PL composition. However, this protective effect may be related to other factors including the presence of the antioxidant tertiary butyl hydroquirone in the purified diets.

212 A SIMPLE NON-INVASIVE TECHNIQUE TO MEASURE INTRA-ABDOMINAL PRESSURE. K.M. Kelly*, T.J. Iberti, D.R. Gentili*, E.Benjamin. Departments of Surgery & Anesthesiology, The Mount Sinai Medical Center, One Gustave Levy Place, New York, N.Y. 10029.

Increased intra-abdominal pressure (IAP) may occur in a variety of shock states, and may interfere with cardiac, renal, and respiratory function. IAP is infrequently measured due to the need for invasive intra-peritoneal pressure monitoring. The purpose of this study was to evaluate the use of a transurethral bladder catheter as a simple way to measure IAP. Six dogs were anesthetized, ventilated, and hemodynamically monitored. A peritoneal catheter which allowed for direct pressure measurement (IAP) and the infusion of peritoneal fluid, and a transurethral catheter were inserted. Hemodynamics, ABG's, IAP and bladder pressure (BLAD) were recorded as peritoneal fluid was infused. The results show that throughout the range of IAP obtained (9.8-68.8 mmHg) that the BLAD was not significantly different from the IAP. *= $p< 0.05$.

FLUID	0	+3000 ml	+5000 ml
IAP	9.8 ± 4.7	27.2 ± 3.1*	69.8 ± 9.5*
BLAD	9.2 ± 4.5	27.6 ± 2.6*	70.0 ± 5.9*

We conclude that in this model, IAP can be accurately assessed with the use of a simple bladder catheter. If this model has clinical applications, it would facilitate studies evaluating the physiologic effects of increased IAP in critically ill patients.

213 ~ XTRAN FOR TRAUMATIC SHOCK PATIENTS IN SPITE OF POSSIBLE ANAPHYLACTIC REACTIONS ?
H. Laubenthal*, K. Peter*, K. Messmer. Instit. Anesthesiol., Univ. Munich, 8000 Munich 2, W. Germany.

Solutions of dextran 60 or 70 are well-known as excellent plasma substitutes for the first treatment of hypovolemic patients in traumatic shock. However, dextran-induced anaphylactoid/anaphylactic reactions (DIAR) are rare but sometimes fatal; their symptomes range from mild skin reactions (grade I) to cardiac or respiratory arrest (grade IV). Since severe DIAR (grade III + IV) could be classified as immune complex anaphylaxis, the use of the hapten inhibition principle has been proposed for prevention of DIAR. In a prospective clinical multicenter study patients receiving infusions of dextran solutions were pretreated with an i.v. injection of 20 ml of a monovalent haptendextran solution 15%. Results:

nr. of	DIAR nr.	severity degree of DIAR (%)			
patients	total (%)	I	II	III	IV
30903	28 (0,091)	18 (0,058)	7 (0,023)	3 (0,010)	0

As compared to infusions of dextran without hapten prophylaxis (1) the incidence of severe DIAR was reduced from 0,25% to 0,01%. In addition to these results, patients in shock do not need the hapten prophylaxis: the necessary rapid infusion of the dextran solution in shock patients results in an excess of antigen in the blood and therefore prevents the formation of immune complexes and the occurence of anaphylaxis. It is concluded that dextran 60 or 70 is the plasma substitute of choice in shock patients on account of its excellent volume effect and the safe prevention of side effects. Lit.: 1) Gruber UF et al.: Brit. Med. J. 280, 69, 1980

214 **TISSUE SURFACE pH: DIFFERENCE BETWEEN MUSCULAR AND RENAL REPERFUSION IN RESPONSE TO HYPERTONIC RESUSCITATION (NaCl 7.5%) FROM HEMORRHAGIC SHOCK.**
JG Maksoud*, RN Younes* and AAR Ayoub* (Spon M Rocha e Silva). Dept Surgery, Fac Med Un Sao Paulo, Brasil.

Tissue surface pH reflects tissue perfusion and assesses the effectiveness of volume replacement in terms of regional reperfusion of each tissue. This study compares renal and muscular tissue reperfusion, as evaluated by surface pH, after hemorrhagic shock and hypertonic resuscitation (NaCl, 7.5%) in 30 secobarbital (25 mg/kg) anesthetized dogs. Surface pH probes were positioned on the kidney and calf muscle surfaces, dogs were bled to 40 mm Hg over 45 min, then randomly treated with hypertonic (7.5% - HS) or isotonic (IS) NaCl (infused volume: 10% of shed blood - removed blood: 39±4 ml/kg). Table I displays mean arterial pressure (MAP), renal surface pH (RpH), muscle surface pH (MpH) arterial blood pH (BpH) at 0, 45, 75 and 105 min of the study. Regional differences were observed in tissue perfusion after resuscitation with HS, reflected by a significantly higher RpH, but lower MpH, despite the recovery of MAP and BpH. These data confirm previous studies showing increased renal, but low muscular blood flow after HS infusion in hemorrhagic shock.

TIME	MAP		BpH		RpH		MpH	
(min)	HS	IS	HS	IS	HS	IS	HS	IS
0	122±8	135±10	7.23±.05	7.21±.05	7.31±.04	7.28±.05	7.30±.06	7.28±.05
45	40±2	40±2	7.12±.04	7.10±.04	7.15±.05	7.14±.03	7.14±.03	7.06±.07
75	102±3§	73±4	7.12±.05*	7.04±.04	7.20±.05*	7.07±.04	7.09±.06	6.87±.07
105	102±3§	66±4	7.18±.04*	6.98±.05	7.18±.05*	6.98±.05	7.08±.04*	6.85±.07

HS vs IS significant difference: § - $p < 0.01$; * - $p < 0.05$.

215 AN A-V SHUNT FOR VASCULAR ACCESS IN THE RAT.
G. RASCHBAUM, W. HSIA, H. ILLNER*, T. HARNAR AND P. CANIZARO* Texas Tech Univ. HSC, Lubbock, Texas 79430

Increasing restrictions in the use of large animals may establish rodents as the principle animal model. Cannula dead space is a significant factor in delivering substances intravascularly to these small volume animals. Problems with introducing samples past the cannula and maintaining cannula patency led to our use of an A-V shunt in Sprague-Dawley rats (250 to 450 g). Both ends of an 8 cm length of silastic tubing (0.940 mm ID) were sleeved over 2 cm segments of polyethylene tubing (0.965 mm OD) which were then placed in the right jugular vein and left carotid artery. Sample collection or injection was performed by clamping both arterial and venous portions of the shunt and disconnecting a centrally interposed segment of polyethylene tubing. Injections were introduced on the

venous side while blood sampling was performed on the arterial side. Resumption of shunt flow resulted in complete delivery of the injected samples. Shunt patency was maintained from 3 hours to 2 days. Equilibration curves obtained from introducing 125-I albumin and sampling 50 ul blood every 10 minutes for 3 hours demonstrated an average correlation coefficient of 0.949 in 10 rats. Variation in lung water content, determined by wet to dry weight difference, showed no statistical significance in 19 shunted and 16 non-shunted rats at 3 hours. The use of an A-V shunt greatly facilitated complete injection and blood sampling in the rat while producing excellent linearity in albumin equilibration curves. Despite the high output nature of the shunt no increase in lung water content was demonstrated at 3 hours.

216 CHANGES IN ARTERIAL BLOOD GASES, TEMPERATURE, AND PLASMA LACTATE CONCENTRATIONS IN RATS EXPOSED TO INTRAVENOUS OR AEROSOL T-2 MYCOTOXIN. C. B. Templeton and D. A. Creasia*. Pathophysiology Division, USAMRIID, Ft. Detrick, Frederick, MD 21701.

The effects of an LD_{99} aerosol exposure of T-2 mycotoxin on arterial blood gas and plasma lactate values were compared to effects seen with intravenous (IV) injection. Sprague-Dawley rats (male, 300-350 g) were randomly divided into four groups of eight animals each. Two groups were exposed to aerosolized T-2 mycotoxin (650 g/L) or saline vehicle for 10 minutes. The other two groups were injected IV with either T-2 (1 mg/kg) or saline. After rats were exposed to toxin, samples were taken for determining blood gases and plasma lactate concentrations at 0, 0.5, 1, and 1.5 and each additional hour until 24 hours or death. Core body temperatures were also recorded at these times. Four hours after exposure, rats exposed to aerosol toxin began to show increased pO_2 and decreased pCO_2 and pH values. Body temperature decreased markedly from 37°C to 28°C. Additionally, plasma lactate values increased to nearly 8 times that of baseline. Previous data show a very similar pattern in the IV-exposed animals. All rats exposed to aerosol T-2 toxin died between 9 and 11 hours (mean time to death = 10.2 hours). The saline-treated rats showed no significant changes in either the blood gases or the plasma lactate concentrations throughout the 24-hour period. We observed that rats exposed to T-2 mycotoxin at the doses given develop hyperoxemia, hypocarbia, a shift toward anerobic metabolism and partially compensated metabolic (lactic) acidosis and subsequently die before 11 hours. We hypothesize that these events are a result of inhibition of oxygen utilization.

217 THERMAL INJURY AND DENERVATION INDUCE SIMILAR CHANGES IN MUSCLES' RESPONSE TO INSULIN. J. Turinsky, Albany Medical College, Albany, NY 12208.

Previous studies from this laboratory have shown that 3 days after a single hindlimb scald in the rat, muscles of the burned limb, but not the contralateral unburned limb, are resistant to insulin. Soleus muscle of the burned limb is completely unresponsive to insulin, whereas burned limb plantaris muscle responds to the hormone but the magnitude of the response is reduced. The aim of the present study was to test whether the changes after burn injury could be due to thermally-induced denervation. The rats were denervated on one hindlimb by sectioning the sciatic nerve. Three days later, the rats were injected i.v. with 2-deoxy-[1-^{14}C]glucose (DG) with or without 0.1 U insulin/rat and cellular uptakes of DG by soleus and plantaris muscles in vivo were determined during the subsequent 25-min period. The denervated soleus muscle had the same basal DG uptake as the contralateral sham counterpart. Exogenous insulin increased DG uptake by the sham soleus muscle 533% but had no effect on the denervated soleus muscle of the same animal. Denervated plantaris muscle exhibited a 272% elevation in basal DG uptake compared with the sham plantaris muscle. In the presence of exogenous insulin, DG uptake by sham and denervated plantaris muscles was increased to the same absolute level. However, the absolute increment in DG uptake induced by insulin was 67% lower in the denervated plantaris muscle compared with its sham counterpart. It is concluded that denervation-induced changes in the response of muscles to insulin are similar to those after the hindlimb scald. (Supported by USPHS grant GM-22825)

218 INTERRELATION BETWEEN BODY TEMPERATURE DURING EXTRACORPOREAL CIRCULATION AND THE LETHALITY OF ENDOTOXIN SHOCK. T. Yoshioka*, T. Tani*, T. Oka*, K. Hanasawa*, Y. Endo*, K. Matsuda*, K. Numa*, Y. Kuniyoshi*, Y. Ishii* and M. Kodama* (Spon : H. Hirasawa).
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Objects : The first was "to know the influence of body temperature (BT) on the biological reactions during and after extracorporeal circulation (ECC)". The next was "evaluating the effects of ECC on defense system of animal".

Methods : Twelve adult mongrel dogs were divided into two groups as preserved body temperature group (PBT) and non-preserved body temperature group (non-PBT). ECC consistent of on-line plasma separation and reinfusion was carried out on dogs (Sham plasmapheresis). This system is made up clinically using blood tubes for plasma exchange and hollow fiber membrane plasma separator (PEX-50, Nipro Med.). In the PBT, Plasma separator and circuit except for pump were kept warm at the same temperature of BT (39 C) in the water bath, and it was not done in the non-PBT. Following 180 minutes of ECC, 2 mg of E. coli endotoxin (Difco Lab.) per kg body weight was infused into dogs of both groups.

Results : 1)BT : In the PBT, their BT were kept within normal range (<1.0 C). But dogs in the non-PBT showed marked decline of BT (>4.0 C). 2)White Blood Cell (WBC) : There was a subsequent recovery and rebound of WBC count in the PBT. While, there was no recovery of WBC in the non-PBT. 3)Survival rate : In the PBT, only one dog out of six survived. But all of six dogs in the non-PBT survived more than 72 hours.

Body temperature of experimental animals during ECC affected their biological reaction and recovery from endotoxin shock.

219 CAROTID SINUS SENSITIVITY IN ENDOTOXIN SHOCK. F. L. Abel and R. F. Bond. Depts. of Physiology, University of South Carolina Sch. Med., Columbia, SC 29208 and Oral Roberts University Sch. Med., Tulsa, OK 74171

Activity of the sympathetic nervous system is decreased in endotoxin shock as evidenced by decreases in renal nerve activity and by decreases in blood pressure when cardiac output is maintained constant with a pump. The decrease in sympathetic activity in endotoxin shock contrasts with that in hemorrhagic shock and could be related to a direct effect of endotoxin on the central nervous system or to a change in sensitivity of the baroreceptors, i.e. the baroreceptors could have an increased sensitivity. These experiments were designed to investigate the gain of the carotid baroreceptors following endotoxin. In mongrel dogs, anesthetized with sodium pentobarbital, a pump was used to supply arterial blood to the isolated carotid sinus, thus providing a means of altering carotid sinus pressure while maintaining carotid body perfusion. A shunt to the jugular vein permitted altering sinus pressure without loading the systemic circulation. After bilateral vagotomy, to remove the aortic arch baroreceptors, step changes in carotid sinus pressure were monitored for their effects on heart rate, arterial pressure, and femoral vascular resistance. Administration of 1 mg/kg E. coli endotoxin (Sigma) produced a typical hypotensive response which was followed for 1 hour, then treated with 10 mg/kg ibuprofen. Although the responses were dependent on the absolute values, e.g., the arterial pressure response depended on the arterial pressure, the responses to changes in carotid sinus pressure were basically unchanged by endotoxin. (Partially supported by S.C. Heart Assoc.)

220 EFFECT OF SYSTEMIC ARTERIAL PRESSURE ON CEREBRAL BLOOD FLOW IN RABBITS AFTER 4-VESSEL CERVICAL OCCLUSION. D.F. Peterson*, M.S. Claussen* and S.L. O'Dell* (Spon. R.F. Bond)
Oral Roberts University School of Medicine, Tulsa, OK 74171.

Eighteen New Zealand white rabbits were anesthetized with Nembutal and instrumented for injection of radiolabeled microspheres. Blood pressure (BP), blood removal and blood samples were obtained from femoral arteries. The right common carotid artery (midcervical) and vertebral arteries (at their origin) were isolated and looped for later ligation. Microspheres were injected into the left vertricle via a left carotid artery catheter under the following experimental conditions: one carotid occluded (BL) (BP=90±5 mmHg): both carotids occluded (2C) (BP=119±12 mmHg); all 4 cervical vessels occluded and, i) BP not controlled (124±9 mmHg) (4V-H), ii) BP controlled near BL (104±6 mmHg) (4V-N); iii) BP reduced (59±6 mmHg) (4V-L). Tissues studied included; bilateral samples of brain stem, cerebellum, cerebrum, eyes, masseter muscles and kidneys as well as heart, tongue and cervical spinal cord. 2C reduced flow

to eye, masseter and tongue. Four vessel occlusion always reduced flow to all tissues measured except heart and lower cervical spinal cord. No changes in flow to any region of the brain were observed when comparing 4V-H to 4V-N. Under these conditions brain flow remained at near 50% of BL (4V-R, 36-63%; 4V-N, 45-66%). Under condition 4V-L, flow to all regions of the brain was lower than during any other condition (14-24% of BL). Calculated conductances revealed that no differences existed between BL and 2C. 4-vessel occlusion at any BP caused a significant fall in conductance which was not further altered by differences in BP. These data indicate that during 4-vessel occlusion brain blood flow is seriously compromised and extremely vulnerable to further decreasing blood pressure below baseline.

221 TOXICITY OF HIGH DOSE NALOXONE. W. Barsan*, C. Olinger*, H. Adams*, R. Eberle*, T. Brott*, J. Biller*, M. Biros* (Spon: D. Reynolds), University of Cincinnati, Cincinnati, Ohio 45267, University of Iowa, Iowa City, Iowa 52242.

The effects of high-dose Naloxone in humans have not been extensively studied. We treated 38 patients with acute ischemic cerebral infarction with high doses of Naloxone to evaluate potential efficacy and toxicity. All patients had cerebral infarction within 48 hours of study entry. Mean patient age was 62.8 years. Excluded were patients < 35 years old or > 85 years old, patients with coma, pregnancy, renal failure, hepatic failure, seizures, and sustained mean arterial pressure > 140mm Hg. Head CT scans were obtained prior to study entry to exclude hemorrhage. All patients were treated with a 160 mg/M^2 loading dose followed by 80 mg/M^2/hr x 24 hours. There were no significant changes in mean arterial pressure, respiratory rate, or heart rate in response to the loading dose or infusion. 23 patients had adverse reactions possibly related to Naloxone. The most common was nausea (n=20) which required treatment in 18 patients. Vomiting occurred in 13 patients. Seven patients had the drug discontinued for possible toxic side effects: focal seizures (n=2), myoclonus (n=1), bradycardia and/or hypotension (n=3), and hypertension (n=1). All patients responded to discontinuation of Naloxone and pharmacologic therapy when indicated. There were no deaths attributable to Naloxone treatment. Three patients developed transient mild elevation of liver function tests which returned to normal within 7 days. No patients were clinically jaundiced. High dose Naloxone appears to be well tolerated in elderly patients with acute cerebral infarction.

222 PARASYMPATHETIC NERVOUS SYSTEM (PNS) INVOLVEMENT IN CANINE ENDOTOXIN SHOCK. C.A. Gray*, C.D. Williams*, L.O. Lutherer, and H.F. Janssen. Orthopaedic Surgery & Physiology, Texas Tech Univ. Hlth. Sci. Cntr., Lubbock, TX 79430.

Evidence suggests that the autonomic nervous system response to hypotension is blunted during endotoxin shock. Information regarding PNS activity in shock is minimal; however, several reports have indicated that it may depress cardiovascular function and that blockade of this system may help maintain mean arterial pressure (MAP). The current study explored this possibility in the pentobarbital-anesthetized (30 mg/kg) canine, endotoxin shock model (0.5 mg/kg-Difco Labs E. coli 055:B5). The MAP response of intact dogs was compared with that of animals having undergone cervical vagotomy, diaphragm vagotomy, or atropine pretreatment (0.5 mg/kg bolus + 0.25 mg/kg/hr). In addition, the reflex heart rate change that normally accompanies rapid MAP decrease was compared between these animals and a separate group which received nitroprusside (3 mg/kg bolus). Statistical analysis was used to compare the groups and significance was accepted at $p < 0.05$. The results suggest that removal of PNS influence on the heart by vagotomy or atropine administration does not significantly alter the MAP response induced by endotoxin bolus. During endotoxemia, the reflex cardioacceleration produced by the initial rapid depression of MAP was present at 25-50% of maximum hypotension but disappeared at more severe hypotension. Inhibition of the PNS did not reverse failure to maintain the cardioacceleratory reflex. These results suggest that the PNS is not significantly involved in the early hypotension produced by a bolus endotoxin injection in the canine model. Supported in part by NIH grant #GM35186.

223 REPERFUSION INJURY OF THE BRAIN AFTER TEMPORARY OCCLUSION OF THE MIDDLE CEREBRAL ARTERY: EFFECT OF GANGLIOSIDE TREATMENT. J. Hamar*, J.H. Greenberg*, M. Reivich* and R. Urbanics*. (Spon: R.J. Alteveer) University of Pennsylvania, Philadelphia, PA 19104.

Experiments were carried out on 30 anesthetized and artificially ventilated cats. The left MCA was occluded for two hours, after which the clip was removed and the tissue was allowed to be reperfused for four hours. Measured parameters included bilateral EEG, cortical blood flow (H_2 clearance from two surface electrodes on ischemic side), extracellular K^+ activity (microelectrodes on stroke side), pH and blood gas, and end-tidal CO_2. Severity of tissue ischemia was based on the depression of EEG amplitude. Fifteen animals were given a synthetic ganglioside (AGF-2) at a dose of 5 mg/kg 30 min. after occlusion while the remainder of the animals served as controls. Arterial blood pressure increased from a control value of 120 mm Hg to 150 mm Hg by the end of the experiment. Cortical blood flow was reduced to 30% (30 ml/min./100g) of control in the first 30 min. and started to recover during ischemia only in the mild groups. In the reperfusion period, flow returned to preocclusion levels only in the mild stroke cases treated with AGF-2 but not in the moderate and severe cases. Extracellular potassium concentration increased 40-45 mM above control levels in the moderate and severe, and to 10mM in the mild groups, respectively, in the first 30 min. of ischemia. Potassium activity decreased toward the end of the occlusion period although preocclusion levels were reached in the mild groups only. These changes in potassium were not affected by the AGF-2 treatment. A more complete reperfusion in the mild stroke groups suggests a potential benefit of this drug.

224 BENEFICIAL EFFECT OF THE TRH ANALOG CG-3703 ON HYPOTENSION AND NEUROLOGICAL DEFICIT CAUSED BY TRAUMATIC BRAIN INJURY IN RATS. T. McIntosh, R. Vink*, J. Watson*, S. Fernyak* and A. Faden. Center for Neural Injury, University of California, San Francisco, CA 94121.

Traumatic injury to the central nervous system (CNS) may cause cardiovascular changes through the release of endogenous factors, including endogenous opioids. Antagonism of such factors may therefore serve to limit the extent of injury and improve outcome. Thyrotropin-releasing hormone (TRH) can antagonize certain physiological effects of endogenous opioids without altering analgesia. The present study compared the effectiveness of a centrally-active TRH analog CG-3703 in the treatment of fluid-percussion (FP) brain injury in rats. Fifteen minutes following brain injury (2.1 - 2.8 atm), anesthetized rats were randomly assigned to treatment with an IV bolus of either CG-3703 (1 mg/kg, n=8) or saline (equal volume, n=8). Changes in mean arterial pressure (MAP) were recorded over a 2 hour postinjury period. Animals were allowed to recover and chronic neurological scoring was performed daily for 4 weeks postinjury. FP brain injury induced a significant fall in MAP by 30 minutes and a 58% mortality rate in saline-treated animals ($p < 0.05$). Administration of CG-3703 caused a significant increase in MAP within 15 minutes (mean increase = 20 mm Hg, $p < 0.05$) that was maintained for up to 2 hours. All animals treated with CG-3703 survived. FP brain injury also produced a chronic neurological deficit in surviving saline-treated animals which was significantly reduced in animals receiving CG-3703 ($p < 0.05$). These results suggest that centrally-active TRH analogs may be effective in the treatment of hypotension, neurological dysfunction and mortality associated with acute head injury.

225 **HYPEROSMOTIC SODIUM SALTS FIRE AFFERENT VAGAL ACTIVITY IN RATS; OTHER SOLUTES ARE INEFFECTIVE.** M. Rocha e Silva, E.D. Moreira*, E.M. Krieger* and Rose I. Noqueira da Silva*. Instituto do Coração, Fac. Med. Un. São Paulo, 05403, São Paulo, Brasil.

Hypertonic Na^+ salts treat severe hemorrhage, but other solutes are ineffective. Survival, high cardiac output and venoconstriction depend upon pulmonary vagal innervation. The effects of hypertonic (2400 mOsm/l, 4 ml/kg) Na^+ salts (chloride, bicarbonate, acetate), chlorides (lithium, tris) and non-electrolytes (glucose, urea), on afferent multifiber activity of cervical vagi in pentobarbital (40 mg/kg) anesthetized rats are described. Fibers with typical Hering-Breuer (HB) activity were selected for recordings. Na^+ salts increased firing rates during HB cycles from 70 ± 6 to 165 ± 11 spikes/sec, 30 sec after the bolus. Five min later HB firing rates remained high at 215 ± 23 spikes/sec, with no differences between the salts. The normally silent interval (INT) between HB cycles exhibited intense activity after Na^+ salt injections, rising from 6 ± 2 to 98 ± 13 spikes/sec, at 30

sec, no differences between salts. High INT activity lasted longest (8-20 min) after acetate, least (2-4 min) after bicarbonate. Tris Cl^-, LiCl, glucose and urea were entirely without effect on HB or INT firing rates. These results correlate with long term survival observed in hypertonic resuscitation experiments in dogs. Na^+ salts produce survivals in excess of 60% (NaCl: 98%; acetate: 72%; bicarbonate: 61%) while the other solutes induce rates lower than 33% (urea: 33%; tris: 22%; glucose and LiCl: 5%). **CONCLUSIONS:** Hypertonic Na^+ salts evoke activity in pulmonary afferent fibers, associated with cardiovascular adjustments and partially responsible for the survival rates observed following hypertonic resuscitation.
(Research supported by Fundação E.J. Zerbini, FINEP and FAPESP.

226 FIBRONECTIN SYNTHESIS BY HEPATIC KUPFFER CELLS ISOLATED FROM ENDOTOXIN-TREATED RATS. P. Vincent, E. Cho and T. Saba. Albany Medical College, Albany, NY 12208.

Low dose endotoxin infusion into rats at a dose that elicits resistance or tolerance to shock produces a marked elevation (80-90%) of circulating plasma fibronectin (Fn). Elevated plasma Fn augments reticuloendothelial phagocytic function and may influence vascular integrity, both of which may be important to tolerance. While hepatocytes are believed to be a major site for synthesis of plasma Fn, other cell types such as macrophages also synthesize opsonically-active Fn as well as increase their production of Fn upon exposure to inflammatory agents. In this investigation, Kupffer cells obtained from rats treated i.v. with S. enteritidis endotoxin (100 ug) for 3 consecutive days were used to quantify Fn synthesis. Kupffer cells were isolated from livers on day 4 by pertusion with .03% collagenase followed by a 1 hr incubation in 0.2% pronase-0.1% DNAse solution. Kupffer cells were separated from parenchymal cells using metrizamide gradient centrifugation and cultured at a density of $2x10^6$ cells/16 mm tissue culture well in DMEM with 10% calf serum. Quantitation of Fn by ELISA showed that Fn concentration in the culture medium increased significantly ($p < 0.05$) from 208±35 ng/ml at zero time to 548±91.9 ng/ml at 24 hrs; 873.8±355.8 ng/ml at 48 hrs; and 1541±292.4 ng/ml at 72 hrs. SDS-PAGE coupled with immunoblot analysis revealed that Fn in the media at 24, 48, and 72 hrs was intact (MW-440 kd) with minimal fragmentation. Thus, Kupffer cells isolated from endotoxin treated rats synthesize and release large amounts of Fn which may contribute to its elevation following low dose endotoxin challenge. (GM21447; HL07194)

227 **HYPERTONIC SALINE DEXTRAN SOLUTION FOR RESUSCITATION AFTER HEMORRHAGIC HYPOTENSION.** U. Kreimeier*, UB. Brückner*, M. Schoenberg*, J. Schmidt*, K. Messmer.
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Small-volume substitution using hypertonic saline has been proposed for initial resuscitation after hemorrhagic hypotension. Our aim was to study the **macro-** and **micro-**hemodynamic effects after 45 min of hypotension by volume resuscitation with hypertonic **and** hyperoncotic solutions **(HSS). Method:** 18 beagles, anesthetized (pentobarbital, controlled ventilation), were bled to a MAP of 40 mm Hg, which was maintained for 45 min. Within 2 min **10 %** of the shed blood volume (avg= 39 ml/kg bw), were substituted by iv infusion of: a) 10 % Dextran 60 in 7.2 % NaCl (n=6); b) 10 % Dextran 60 in 0.9 % NaCl (n=6); or c) 7.2 % NaCl alone (n=6). At control, end of hypotension, 5 and 30 min after volume resuscitation central hemodynamics, extravascular lung water (EVLW) and regional blood flow (RBF; 271 samples from 11 organs; radioactively labeled microspheres Ø 15 µm) were measured. **Results:** Restoration of cardiac output was observed within 5 min in all animals treated with **hypertonic** solutions, accompanied by a decrease in total peripheral resistance. MAP reached only 50 % of control values. EVLW remained in control range of 6 to 8 ml/kg in all groups. O_2-availability was highest in animals treated by **HSS.** RBF was decreased at the end of the hypotension period in all organs except left ventricle, brain and adrenals. Though primary volume substitution consisted of 10 % of the shed blood only, RBF in brain, heart, kidneys, small intestine, colon, and liver was in the control range after infusion of **HSS.** RBF in pancreas and gastric mucosa remained reduced in all groups. **Conclusion:** Small-volume resuscitation with hypertonic-hyperoncotic solution represents a powerful tool for immediate restoration of cardiovascular function after hemorrhagic hypotension. The initial circulatory effect of hypertonic saline infusion was increased **and** prolonged by combination of 7.2 % saline with 10 % Dextran 60.

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